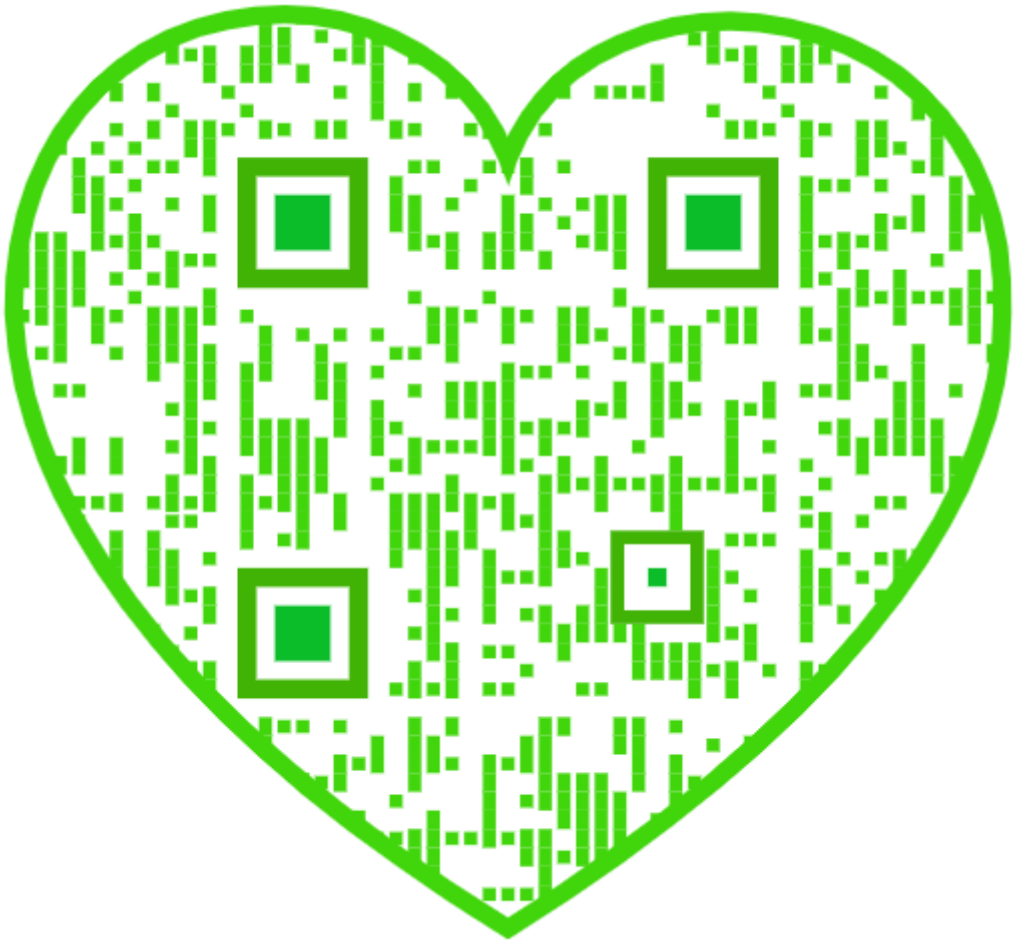

TYPHOID FEVER

CONSIDERED AS A PROBLEM OF SCIENTIFIC MEDICINE

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TYPHOID FEVER

CONSIDERED AS A PROBLEM OF SCIENTIFIC MEDICINE

BY

FREDERICK P. GAY

PROFESSOR OF PATHOLOGY IN THE UNIVERSITY OF CALIFORNIA

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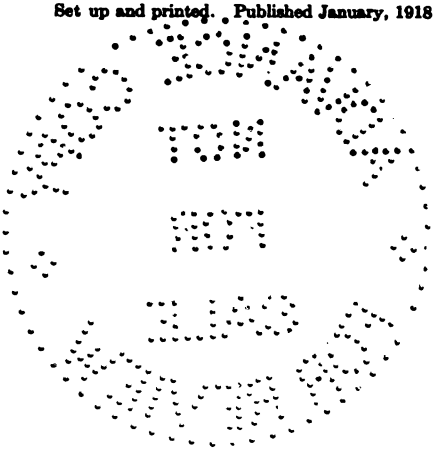

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PREFACE

This treatise is an attempted exposition of the problem of typhoid fever. It aims to treat historically the development and present status of our knowledge concerning this important malady as viewed from the standpoint of its mechanism. It is not primarily designed to aid directly in the clinic or the laboratory, but should serve to point out the relations of one to the other, to indicate the dependence of practice on theory, and the happy applicability to human need of investigation that may have seemed to aim merely at the gratification of intellectual curiosity.

There are numerous admirable clinical treatises on typhoid fever, such as those of Curschmann, of Vincent and Muratet and of McCrae. The purely laboratory and the public health aspects of the disease are well summarized in such works as those of Kutscher, of Chapin and of Whipple. This book aims to strike a balance between these sources of information, following the life history of the typhoid bacillus rather than the manifestations of the disease it produces, in order to gain insight into the nature of the problem as a whole.

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No attempt has been made to make this work encyclopedic in character, although the references to original sources are sufficiently ample to lead a prospective investigator to full sources of information. Although we may have succeeded in maintaining correct proportions in our estimate of the accuracy and value of facts, methods and theories that have been shaken down by time into their proper relations to one another, we shall unconsciously or wilfully have exaggerated the importance of recent contributions. We may well have overemphasized the importance of modern investigations in respect to antityphoid vaccination and specific therapy in typhoid fever through personal enthusiasm. The data on these aspects of typhoid fever are so ample and so recent that a critical summary of their essentials seems desirable, even though somewhat premature.

In addition to the use that has been made of all the general treatises and original sources of information to be cited, particular indebtedness is felt to Charles Murchison's "Treatise on the Continued Fevers" as furnishing the backbone of the discussion of the earlier historical aspects of typhoid fever. The author wishes to express his thanks to Dr. John N. Force, Miss Ruth Stone and Miss Helen Dunbar for suggestions and aid in preparing the manuscript.

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TYPHOID FEVER

CONSIDERED AS A PROBLEM OF SCIENTIFIC MEDICINE

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TYPHOID FEVER CONSIDERED AS A PROBLEM OF SCIENTIFIC MEDICINE

CHAPTER I

A GENERAL SURVEY OF THE DEVELOPMENT OF KNOWLEDGE CONCERNING TYPHOID FEVER

Progress in medicine depends on the gradual recognition and separation of disease entities. Differential diagnosis must precede all rational means of prevention and therapy, and in each of these phases of progress the older methods of bedside observation and experience have been increasingly supplemented by methods of laboratory precision. No disease illustrates better the successive stages of scientific medical advance than typhoid fever, which as a cause of death and economic loss has been one of the world's greatest scourges. A survey of the useful knowledge that we have gained in respect to this disease is at once of historic interest, as bearing on medical progress, and of promise to those who trust in "Man's redemption of man."

PROGRESS IN THE DIFFERENTIAL DIAGNOSIS OF TYPHOID ON THE BASIS OF SYMPTOMATOLOGY AND MORBID ANATOMY

The disease we now recognize as typhoid or enteric fever is one of those continued fevers which was for centuries confused with other lasting fevers of somewhat similar appearance. Even today mistaken diagnoses are frequent, unless the most modern methods of laboratory aid are resorted to. Among those fevers which may be confused with typhoid may be mentioned recurrent fever, septic infection, malaria, tuberculosis, trichiniasis, and, particularly, typhus fever. The recognition of a disease entity like typhoid is, of course, more readily made in face of an epidemic than in an individual case. In the gradual differential recognition of typhoid fever we find certain characteristics which have been evident from the first. One of the most striking things about typhoid fever is its seasonal occurrence, and we find that Hippocrates, in the course of two successive autumns, met with many cases of a fever

of the continuous type, characterized by diarrhea, offensive watery stools, bilious vomiting, tympanites, abdominal pain, red rashes, epistaxis, sleeplessness, and in some cases a tendency to coma, delirium and subsultus, irregular remissions, and a lengthened duration, accompanied by increasing emaciation. Galen classified under the larger grouping of Hemitritœus a variety of bilious fever which may also have been typhoid.

We may continue our historical survey by dividing the criteria of differentiation into two rather arbitrary groups. First of all, may be cited those criteria which are based on purely clinical, observational grounds, and on the basis of experience, and, secondly, those criteria which depend on the recognition of definite changes in anatomic structure. It is obvious that chronologically these two groups of observations will overlap to a considerable extent, but the separation may serve to show the limitation of each type of investigative procedure.

Following the observations of Hippocrates and Galen, which have been mentioned, Spigelius in 1624 noted the occurrence of a fever characterized by the presence of abdominal pain, diarrhea, with sometimes melena, absence of crisis, and occasional relapses. In 1659 Thomas Willis [1] of England was first to make an attempt at separation of typhoid fever from typhus or *febris pestilens*, with which it was still destined for many years to remain confused. He made his differentiation on the basis of the fact that typhoid fever is less contagious, has little or no eruption, an imperfect crisis, and is prone to local complication. In 1734 Ebenezer Gilchrist described typhoid fever under the name of "nervous fever," which he characterized by its long duration, the occurrence of diarrhea, abdominal pain, blood in the stools, epistaxis, and "partial sweats which gave no relief." A further and more complete separation between typhus and typhoid fever was made by Langrish in the following year, who separated the two diseases under the headings of "slow, nervous fever," and "malignant, continued fever." A further amplification of this separation was made by Huxham (1739), who described the two fevers as "slow, nervous fever," on the one hand, and "putrid, malignant, petechial fever," on the other. About the year 1850 a discussion arose between Sir John Pringle and Professor De Haen of Vienna, in reference to the advisability of bloodletting in fevers. This discussion is now of no particular interest as bearing on treatment, but served to bring forward a point in differential diagnosis between the eruptions of typhus and of typhoid. It appears that Pringle was describing bloodletting in typhus fever, whereas the cases

which De Haen had treated were typhoid. It remained for Pringle to recognize the fact that they had been describing two different forms of disease, and he makes the statement that the miliary fever or typhoid of De Haen occurs in all ranks of people and is characterized by a petechial and miliary eruption, whereas the fever which he had been studying, the malignant fever, occurs only among people who are crowded together in such close and foul places as military hospitals, jails, and transport ships. In 1772 Dr. Macbride of Dublin spoke of "febris nervosa," a protracted fever attended by diarrhea, as different from the putrid, continual fever which was contagious and accompanied by a florid eruption which gradually passed into petechiæ.

We may now turn to the differentiation of typhoid fever on the basis of changes in anatomic structure, at once a surer and more scientific basis of classification. It appears that the lesions of typhoid fever were first referred to by Spigelius in 1624, who called attention to an inflammation and sometimes gangrene and sphacelus of both large and small intestines. In 1682 Willis [2] made these observations much more definite by describing, in the less contagious of the two diseases which he attempted to differentiate, pustules like those of variola and ulcers in the small intestines, accompanied by swelling of the mesenteric nodes. In 1696 Baglivi called this fever "febris mesenterica" on account of the enlargement of the mesenteric glands which he found associated with the intestinal inflammation. He also separated the disease from typhus or febris pestilens. Hoffmann in 1699 described gangrene and sloughing of the small intestine as associated with typhoid. Lancisi in 1718 first described typhoid perforation, which, however, he incorrectly attributed to the presence of certain lumbricoid worms in the intestines. In a form of fever which he refers to as Lent or symptomatic fever, Strother in 1729 described inflammation and an "ulcer fixed on some of the bowels." The characteristic lesions of typhoid were more definitely localized by Riedel in 1748, who described "febris intestinalis," accompanied by gangrene of the lower ileum. A definite and full description of the characteristic intestinal lesions of typhoid fever is usually attributed to two German investigators, Roederer and Wagler (1762). After a careful inspection of the original treatise, we agree with Murchison, however, that it is practically certain that these investigators were not dealing with typhoid at all. In their thirteen cases, the post-mortem appearances of which are described with great minuteness, we find no description of ulceration of the ileum, whereas the lesions described are almost entirely

confined to the stomach or to the large intestines. It is probable, then, that the German investigators were in reality dealing with an epidemic of typhus, complicated by dysentery, as Murchison has suggested. It appears that the intestinal lesions of typhoid did not escape the keen observation of John Hunter, as is shown by two preparations in his museum at the Royal College of Surgeons, one of which was later figured in a publication by Matthew Baillie.

It remained, however, for a group of French investigators in the early part of the nineteenth century to describe with fullness and accuracy the lesions which we now recognize as being characteristic of typhoid. In 1804 Prost described ulcerations in the mucosa of the intestines and also a mild type of inflammation, which, however, was in all probability a simple post-mortem change. In 1813 Petit and Serres described in their "Fièvre entéro-mesenterique" lesions which were limited to the lower ileum and were specific, differing in many particulars from the ordinary type of inflammation which occurs in simple enteritis. They believed, moreover, that these lesions preceded and were the cause of this fever. In 1826 Bretonneau described typhoid under the name of "dothienenteritis," which he found characterized by lesions localized in the agminated and solitary glands of the ileum. He thought, moreover, that this disease was due to a poison, transmissible from the sick to healthy individuals, which suggestion may be regarded as the first definite contribution to the means of transmission in typhoid fever. Bretonneau further made the important observation that there is no definite relation between the severity of the disease and lesions produced. These observations were confirmed and amplified in the same year and independently by Hewitt of London, who also described the lesions of the solitary and agminated follicles. The further observations of Louis in 1829 and of Chomel (1834) served still further to separate typhoid from simple gastro-enteritis, and also to point out the lesions of the lymph follicles.

We find, then, at the beginning of the nineteenth century that a pretty clear picture of typhoid fever had been developed, at first on clinical grounds, and later on the basis of post-mortem appearance. There remained, however, for several years confusion between the two diseases, typhus and typhoid, owing largely to the fact that few observers had been able to compare them at first hand. We have mentioned the criteria of differentiation on a purely clinical basis by Willis and Huxham, and other similar observations were also made by Hildenbrand in Germany in 1810, who separated

"contagious typhus" from "non-contagious, nervous fever," a separation which was further amplified by the work of Schoenlein in 1839, who gave names to the two diseases, which still unfortunately persist in Germany, namely, "typhus exanthematicus" and "typhus abdominalis." The objection to these terms lies not in their original form but in the abbreviation of "typhus," which is frequently used indiscriminately for typhus and typhoid.

The valuable anatomic work of Bretonneau, Louis, and Chomel was not immediately of great service in the separation of typhus from typhoid, owing to the fact that the French investigators had no opportunity of studying typhus fever, a disease which in their time prevailed primarily in England. They were, indeed, inclined to regard typhus in England as identical with the French typhoid fever, and they regret that no careful anatomical observations were made by the English observers. Dr. H. P. Lombard of Geneva in 1836, on the basis of study of fever both in France and England, concluded that in England there were two types of disease present: first of all, the contagious typhus; and, second, a sporadic disease identical with the typhoid fever of the French. It remained, however, for William Gerhard in 1837 to establish beyond doubt the differential criteria between typhus and typhoid fever, on the basis of his own experience in both diseases in France and in Philadelphia. Gerhard maintained that the typhus of Philadelphia was identical with British typhus fever and with the jail, ship, petechial or spotted fever, and that it is eminently contagious. On the other hand, the enteric or typhoid fever of the French is rarely communicated from one individual to another. He showed that the lesions of Peyer's patches and of the mesenteric glands invariably present in the latter were never found in the former, and remarked that English observers erred in regarding the intestinal disease as a mere complication of typhus. He insisted on the marked difference between the petechial eruption of typhus and the rose-colored spots of typhoid fever, and he showed that a peculiar train of symptoms very different from those of typhus were associated with the intestinal affection, and that the distinctive characters of the two diseases were such as should not allow them to be confounded in practice. Shattuck of Boston studied cases of both diseases in France and England and separated the two in London. Confirmatory observations were made by Valleix (1839) and by Rochoux (1840) in France, and by Barlow in England (1840). Sir W. Jenner [1, 2] in London between 1849 and 1851 further confirmed and amplified the distinction between the symptoms of the two diseases as previously laid down by Gerhard

and others. By careful analysis of cases admitted into the London Fever Hospital, he showed that the two fevers did not prevail coincidently and that the one did not communicate the other. He also adduced cases to prove that an attack of either fever protected the patient from subsequent attacks of the same malady but not from the other. Perhaps the most important bearing of these facts is their indication that the two diseases are not only different, but are due to distinct causes.

It was possible, then, early in the nineteenth century to recognize typhoid fever as a disease entity on the basis of clinical observation and post-mortem examination. No clear understanding of the exact nature of the disease was, however, possible until the isolation of its specific bacterial cause, nor could the certain recognition of the disease in any particular case be assured in the absence of such knowledge. And, if the individuality and the recognition of typhoid fever is dependent on bacteriology, much more so is accurate knowledge concerning its method of transmission and effective prevention.

DEVELOPMENT OF THE CONCEPTION OF CONTAGION IN TYPHOID FEVER

There were, however, several observations in the pre-bacteriological days which were of extreme significance, and, indeed, of practical importance in understanding and in controlling this disease. Up to the nineteenth century the general belief was that typhoid fever was not contagious. This relative non-contagiousness was, indeed, one of the earlier differential points in diagnosis between typhus and typhoid. Early in the nineteenth century, however, Leuret (1828), Gendron (1834), and Bretonneau (1829) in turn gave definite reasons for regarding typhoid as transmissible from one individual to another. In 1850 Piedvache summarized the facts, and concluded that the disease is to a limited extent contagious. In 1856 William Budd [1] began a series of publications on the nature and mode of transmission of typhoid fever, which constitute one of the most notable contributions to our knowledge of this disease. He not only proved conclusively by careful epidemiological studies that the disease could be transmitted through the feces of a typhoid patient by means of water or milk contamination to healthy individuals, but repeatedly emphasized that this is the usual way in which the disease is propagated. He regards typhoid fever as contagious in the broader sense of the term, using Piedvache's definition that any transmission of a disease from a diseased individual to a healthy individual, what-

ever may be the method, constitutes contagion. The poison of the disease, according to Budd, resides in the diarrheal discharges of the patient, and epidemics are usually caused by contamination of the water supply with such dejecta. "This method of reproduction is not only a characteristic but the master fact in the history of typhoid fever," he says. He discards, after careful discussion, the putrefactive decomposition idea of Pettenkoffer and the pythogenic theory of Murchison, and shows that the disease is essentially self-propagating. He believes he was able to prove this method of contagion, owing largely to the fact that his practice was in the country, where such sewage contaminations are more likely to be traced than with the more complete methods of sewage disposal in cities.

Budd, in addition, laid down definite rules which he proved to be effective in checking and preventing epidemics. It is very interesting, moreover, to find that he distinctly foresaw the possibility of spread of the disease from the dejecta of those who had entirely recovered from any active manifestations of the malady. In view of this now recognized, important carrier condition, it may be of interest to cite his exact words in this connection. Budd says (p. 118): "The precise date at which the fever patient ceases to give fever to others is not so easy to define. But I have seen so many instances in which fever has broken out in a family living in a previously healthy neighborhood soon after the arrival of a convalescent, that I am quite sure that patients so far recovered cannot always be safely allowed to mix with others without precaution. In the case referred to all traces of actual fever had disappeared and diarrhea had long ceased."

Murchison [2] added certain additional facts to the contagiousness of typhoid fever through the feces, although his theory of transmission was marred by the introduction of the idea of a spontaneous origin of the disease through fermentative processes outside the body. He further subscribed to the importance of a transmission of typhoid by means of polluted milk.

Of historical interest in this connection is the so-called ground-water theory of Buhl and of Pettenkoffer in reference to the spread of epidemics of cholera and typhoid fever. The theory, although no longer accepted in its entirety, doubtless throws some light on the spread of certain epidemics of these diseases. According to Pettenkoffer, the contagion of these two maladies would require a ripening stage in the earth, and the actual spread of the epidemic itself depends on the falling of the ground-water with consequent spread of these ripened contagia from the superficial water supplies.

THE ADVENT OF BACTERIOLOGY AND ITS IMPORTANCE IN THE EXPLANATION AND PREVENTION OF TYPHOID FEVER

The year 1880 may be given as marking the advent of the science of bacteriology, and typhoid fever was one of the first of the human infectious diseases to yield the secret of its specific animate causation. In the few years preceding 1880 several observers had described the occurrence of certain micrococci in the tissues of cases of typhoid fever. The bacillus, however, which we now recognize as the cause of the disease was not discovered until 1880. The first observations of Bacillus typhosus in the tissues may be attributed to three independent investigators, namely, Eberth, Klebs, and Koch. Credit of priority in the discovery of the microorganism is generally given to Eberth, but it may well be that injustice has been done in the general acceptance of this priority. It is of interest, therefore, to examine the investigations of these authors in some detail. On April 22, 1880, appeared the first contribution of Klebs [1] on the nature of typhoid, in which he describes his findings in twenty-four fatal cases of the disease. In each of these cases he found short rods, and also in certain places filamentous but unbranching bacterial structures in the various tissues of the body which are peculiarly associated with the malady. He found these organisms in Peyer's patches, in the mesenteric lymph nodes, in the blood vessels, and also in the pia of certain meningeal cases of the disease. The organisms were not found in the intestinal wall of normal cases. They were found in definite relation to what he describes as "a leucocytic proliferation" in the necrotic areas caused by the disease.

In July of the same year Eberth [1] published his findings in typhoid. In the majority of cases of the disease which he investigated he found short bacterial rods in various organs of the body, which diminished in number with the progression of the disease. He states that these rods at times possess spores and do not stain well with the ordinary aniline dyes. From the illustrations which accompany his article it would appear certain that he was dealing with the Bacillus typhosus, although the sporogenous forms which he likewise depicts are misleading. In the year 1881 Koch [1] published photomicrographs of the bacterial findings in various infectious diseases, among them typhoid fever, in which the characteristic microorganism appears with convincing clearness. Both Eberth [2] and Klebs agree that the bacterial or rodlike forms which each of them had in turn described are identical. The

difference in their findings would seem to rest in the description by Klebs of threadlike forms of from fifty to eighty micra in length, which we do now recognize as characteristic of the growth of the typhoid bacillus, at least in the body. Somewhat similar forms have been described in culture media. This type Klebs regards as a second stage in the development of the rodlike form. Klebs may well have erred in describing a type of microorganism which may have been a secondary invader; it is evident, however, that he really did see the same typhoid bacillus that Eberth describes. Since criticism is made of his description of this threadlike microorganism, it may also be pointed out that the sporogenous microorganism described by Eberth is likewise inaccurate. At all events, the threadlike forms described by Klebs seemed to him subsidiary to the rods which alone are mentioned as occurring in the various organs of his twenty-four protocols. Klebs unquestionably should be credited with suggesting the accepted name (B. typhosus) for the etiological agent in typhoid fever.

It would seem also that at least some credit should be given to Klebs for his attempt, and, perhaps, success in cultivating Bacillus typhosus outside of the animal body, although the usual credit for this discovery is given entirely to Gaffky (1884). In Klebs' second communication in 1881 [2] he describes his method of preparing and sterilizing gelatine culture media, his inoculation of such media from the mesenteric lymph nodes of a case of typhoid fever, and he further notes the occurrence of rodlike forms in the turbid culture growth which results from the inoculation. Gaffky objects to accepting Klebs' results largely on the basis that he had described threadlike forms as existing in the disease, and also owing to the fact that he, Gaffky, failed to produce lesions in animals with his pure cultures similar to those that had already been described by Klebs. Klebs had described the production of hemorrhagic infiltration without ulceration in the cecum of rabbits following injection of his culture of the microorganism. Although Gaffky failed to obtain such results with his cultures, it is now known that they may be produced with pure cultures and toxins of the typhoid bacillus, although they are not specific in nature (Arima,[1] Gay and Claypole [1]). Klebs, then, may well have grown Bacillus typhosus and, indeed, may have grown it in pure culture, although it remained for Gaffky to demonstrate the purity of the culture, as he was able to do by the employment of solid culture media. Gaffky remarks on the absence of spores in his artificial cultures of the microorganisms, and also comments on its growth on gelatine and potato.

We have discussed hitherto in some detail the historical development of our knowledge concerning typhoid fever, first on purely clinical grounds, and secondly, on the ground of post-mortem examination. We have further considered the early observations of the typhoid bacillus in the tissues and, secondly, the growth of this microorganism in pure culture. We may now proceed to outline rapidly the successive advances which have followed the complete recognition of a single etiological factor in this disease, leaving more detailed consideration of the method of obtaining such facts and of their significance and applicability to subsequent chapters. It will, we believe, be evident that all significant information concerning the nature of the disease itself and its method of dissemination, as well as all effective means that have been devised to prevent and cure it, have depended on laboratory data and are based on the recognition of the single bacterial causative factor.

Following the observations of Klebs, Eberth, Koch and Gaffky that the typhoid bacillus occurs in the various organs that are obviously affected in the disease, and can be isolated from them in pure culture, it was soon shown by A. Pfeiffer (1885) that the organism could also be found in stools, and by Hueppe [1] in the following year in the urine in typhoid fever.

One of the most important landmarks in the development of our knowledge concerning typhoid fever and in its diagnosis is the detection of the causative microorganism in the circulating blood. Fraenkel and Simmonds [1] (1886) are usually credited with this important discovery. They isolated the organism, to be sure, from the blood of the cadaver in one of six fatal cases in that year, but failed then and the year before to obtain it from the blood of living cases. The presence of the microorganism in the blood post mortem, is of course, of interest, but might well be due to a terminal invasion, and for both diagnostic and etiological reasons the greater importance attaches to the discovery of the bacillus in the blood intra vitam. It is apparently Vilchur who in 1887 was first successful in isolating the typhoid bacillus from the circulating blood, although only in one of thirty-five attempts. Neuhaus had in the previous year obtained the organism from the blood of rose spots in nine of fifteen cases.

It is now generally recognized that typhoid fever is primarily a bacteremia and not a disease essentially characterized by intestinal lesions, which, although they occur in a majority of cases must be regarded rather as incidental and terminal than indications of the true nature of the disease itself. It has already been

pointed out by Louis and others on purely clinical grounds that cases of apparent typhoid fever might occur with absence of any lesions in the intestines. That such cases were indeed typhoid fever and not some disease simulating it, remained, however, to be proven in cases that could be bacteriologically controlled. Such an observation was first made apparently by Terrile, who described a case of typhoid from which he isolated the bacillus in the blood and which showed at death no intestinal lesions. Numerous similar cases have since been described by Chiari [1] and others.

Of great significance was the isolation in 1890 by Gilbert and Girode [1] of the typhoid bacillus from the gall bladder in cases of typhoid with acute cholecystitis. Chiari [2] showed a few years later that the microorganism occurs with great regularity in this viscus during typhoid fever. The relation of these observations to our knowledge of the course of the disease and of its sequels will be fully considered in another place.

By the year 1890, then, it was generally recognized that no disease could properly be called typhoid fever unless the typhoid bacillus was found somewhere in the body; and, conversely, any case having such an organism in the body, or at least in the blood, must be one of typhoid fever.* Another and almost equally valuable method of differential diagnosis was introduced into practice by Widal [1] in 1896.) The characteristic property he found in the blood serum of typhoid cases depends upon the important phenomenon of agglutination. A clumping occurs when the serum of animals that have been inoculated with or infected by a given bacterium is allowed to act on the provocative microorganism.

In the year 1896, Achard and Bensaude reported the first cases which led to separating from the typhoidal fevers a group of maladies now known as paratyphoid infections, similar in most respects clinically to the fever caused by Bacillus typhosus, but each due in turn to a specific microorganism of the paratyphoid or paracolon group. Such organisms, differing in their sugar reactions from true typhoid bacilli, were described in two cases by these French authors and were found in one instance in the urine, and in the other in a parotid abscess. In the following year, 1897, Gwyn isolated a similar "paracolon" organism from the circulating blood of a case, the serum of which agglutinated this organism but not the typhoid bacillus, and thereby proved its etiological relation to the disease.

In the year 1893, Fraenkel made the first attempt to affect

* Exception must be made to the healthy or recovered bacillus carriers.

typhoid fever in a specific manner by the subcutaneous injection of killed cultures of the typhoid bacillus. In 1896, preventive inoculation against typhoid fever was independently attempted by Sir Almoth Wright [1] and by Pfeiffer and Kolle.[1]

Attention may now be drawn to certain observations of significance in relation to the spread of typhoid fever. Reference has already been made to the suggestion of Budd concerning contagion from recovered typhoid cases, and the observations of Klebs [3] in 1887 likewise indicate the danger of infection from the feces of afebrile cases or even of healthy individuals. The danger of feces from cases of typhoid fever in spreading the disease was convincingly pointed out by Reed, Vaughan and Shakespeare in their study of the typhoid epidemics in the Spanish-American War (1898). In their report they point out that the spread of the disease in certain regiments bore an undoubted relation to the carelessness in erecting privies, the exposure of dejecta and the probable rôle of flies that had access to these dejecta in contaminating food supplies. Several observers had shown that flies could mechanically carry bacteria for varying periods of time, and Hamilton finally completed the chain of evidence by showing that flies captured in houses in which there were cases of typhoid actually did carry typhoid bacilli.

In 1898, Petruschy suggested that people who had recovered from typhoid fever might still be able to infect healthy individuals by means of typhoid bacilli that persisted in their urine. Robert Koch (1903) [2] deserves credit for first specifically calling attention to the danger of the extension of typhoid fever through typhoid bacilli in the excreta of convalescents, or possibly of persons who were apparently healthy. This suggestion was confirmed by Frosch in epidemics in southwest Germany, and led to the establishment of many stations there for the study of such ways of disseminating the disease. This study proved not only the relative infectiousness of stools in different periods of the active disease, but demonstrated that the bacilli persist for varying lengths of time in some four per cent of recovered cases. In 1904, Drigalski made the important observation that typhoid bacilli may also be found in the feces of some individuals who have apparently never suffered from the disease and that epidemics may be caused by such "healthy" carriers.

CHAPTER II

TYPHOID FEVER AS A CAUSE OF DEATH AND DISABILITY

Our interest in typhoid fever is manifold and compelling. In the first place, we are humanely concerned with the disease as one of the great causes of death and disability, more particularly in the past, but yet to a considerable extent in the present. And it is precisely this rapidly waning seriousness of typhoid that enhances its interest as a pragmatic problem of preventive medicine. The rapidly increasing group of facts that has been gathered through its scientific study, and particularly during the latter years, has led not only to a gratifyingly complete conception of the disease process itself, but has produced practical results of great significance. No human disease, under varying conditions of life, in war and in peace, has been more rapidly checked, and none gives greater promise of eventual complete suppression.

THE SIGNIFICANCE OF TYPHOID FEVER IN MORTALITY STATISTICS

In the United States, of all nations, our consideration of the typhoid problem is particularly to be desired, since we have hitherto been extremely backward in applying recognized methods of sanitary prevention which have long prevailed in other lands. Typhoid fever remains the ninth contributing cause to the mortality statistics * in this country and ranks fifth among the infectious diseases, being exceeded as a cause of death only by tuberculosis, pneumonia, infantile diarrhea and diphtheria. The economic importance of the disease is even greater than is suggested by these mortality figures, serious as they are, for it is precisely in those years of greatest expectancy and promise that its incidence is greatest. After passing through the perilous years of infancy with its characteristic and as yet not wholly avoidable infections, the child, and particularly the young adult, arrives at a period where his chances of usefulness are found to be most assured, and it is during this period that typhoid is most common. About fifty per cent of all cases of the disease occur between the ages of fifteen and twenty-five, and the greater part of these in

* Dept. of Commerce Mortality Statistics, 1915.

the earlier lustrum (Murchison;[1] Curschmann). Graham, who has studied the incidence of acute infections occurring in children in Philadelphia from 1911 to 1915, finds that typhoid fever ranks next to diphtheria as a cause of death and has the highest mortality rate.

The actual death rate from typhoid in the United States was in 1900, 35.9 to the 100,000 inhabitants, and in 1913, 17.9, an encouraging diminution of over fifty per cent. Most of the other major causes of death have also diminished during this period, with the exception of cancer and certain chronic diseases, but the rapidity of diminution in typhoid fever has been exceeded by only one other acute infectious disease, namely, diphtheria. Any satisfaction we may feel in these results is, however, lessened on considering that our mortality rate in 1900 had not quite reached the low level in Germany in the five years from 1879 to 1883. The actual number of cases of typhoid fever in the United States in the year 1900 is estimated at 353,790 (Whipple), and the deaths were 35,379. In 1914, the number of cases had diminished to 198,000 and the deaths correspondingly to 19,800 (Dublin). In 1912, the death rate in Germany * was three per 100,000, or actually 2,119 deaths, in a population of over 64,000,000. There may be some satisfaction in finding that the United States recently shows a lower typhoid death rate than the two most backward continental nations, Spain and Italy, which in 1912 were twenty-seven and twenty-two respectively. No other European nation, however, exceeded nine (Belgium).

The occurrence of any given disease in a community is usually estimated from the mortality statistics and not from the actual cases that are supposed to exist. In the case of typhoid the death rate is more accurate and complete, owing to possible errors in diagnosis and failure to report cases that do not terminate fatally. It is, therefore, important to know the percentage mortality which is ordinarily to be expected, and it is generally accepted that in typhoid fever the mortality is now about ten per cent. It is interesting in this connection to note that the mortality rate fell markedly in the latter half of the nineteenth century. In Murchison's statistics from the London Fever Hospital it appears that for the twenty-three years from 1848 to 1870 the mortality varied between 15.63 and 26.97 per cent, the latter figure being the one for the year 1848. The average for this period was 17.26 per cent. This may further be compared with statistics which

* Ergebnisse des Todesursachen Statistik im deutschen Reich für das Jahr 1912. Springer, Berlin, 1914.

Murchison gave from the best hospitals in France, Germany and England, which gave a similar average mortality of 17.45 per cent. It is evident, then, that the decrease in mortality, which is due in large part to better care and probably also to lessened virulence of the infection for the individual, or conversely to increased human resistance to this particular disease, must be taken into consideration in estimating the diminution of the disease itself from the mortality statistics. The tendency then in more recent statistics, based on the decreasing mortality rate, is to underestimate the actual number of cases of the disease. It may be noted here that the mortality percentage increases with the age of the patient, ranging from a little over two per cent in infants to thirty-five per cent in adults over forty-five years of age. The mortality is undoubtedly higher in hospitals than it is in those private houses where the best facilities for nursing are available (Jochmann; Brouardel and Thoinot).

CHRONOLOGICAL CHANGES IN THE TYPHOID DEATH RATE

The chronological diminution of typhoid fever has already been suggested. We may express this diminution somewhat more concretely by taking first certain figures collected by Seitz [1] in Germany towards the end of the nineteenth century (Table I).

TABLE I

COMPARATIVE MORTALITY STATISTICS FROM TYPHOID FEVER PER 100,000 OF POPULATION IN GERMANY, BAVARIA AND MUNICH AT SUCCESSIVE PERIODS

	Germany	*Bavaria*	*Munich*
1857–67	—	77	203
1868–78	47	54	123
1879–83	26	26	30

This table, which is representative of many other statistics collected over a similar period, illustrates two important facts from which a great hygienic principle of particular import in typhoid fever and some similar diseases may be deduced. It will be noted, first, that the mortality rate during the greater part of this period was consistently and markedly higher in a city than in the state or empire at large, and, secondly, that a sharp diminution in both city and empire occurred about the year 1880. This diminution, it may be noted, continued until in the period 1901–1910 the mortality rate for Munich averaged 2.5 to the 100,000.

From these and other similar figures the general statement may

be made that prior to a period, roughly about the year 1880, typhoid fever was a disease the incidence of which varied directly with the density of population, as shown by the increased number of cases in a city like Munich as compared with the larger districts of which it formed a part. Further mortality statistics from the same city of Munich, comparing the incidence of the disease in the Munich garrison as against the general city population, still further and in a more concrete manner illustrate the same principle (Table II).

TABLE II

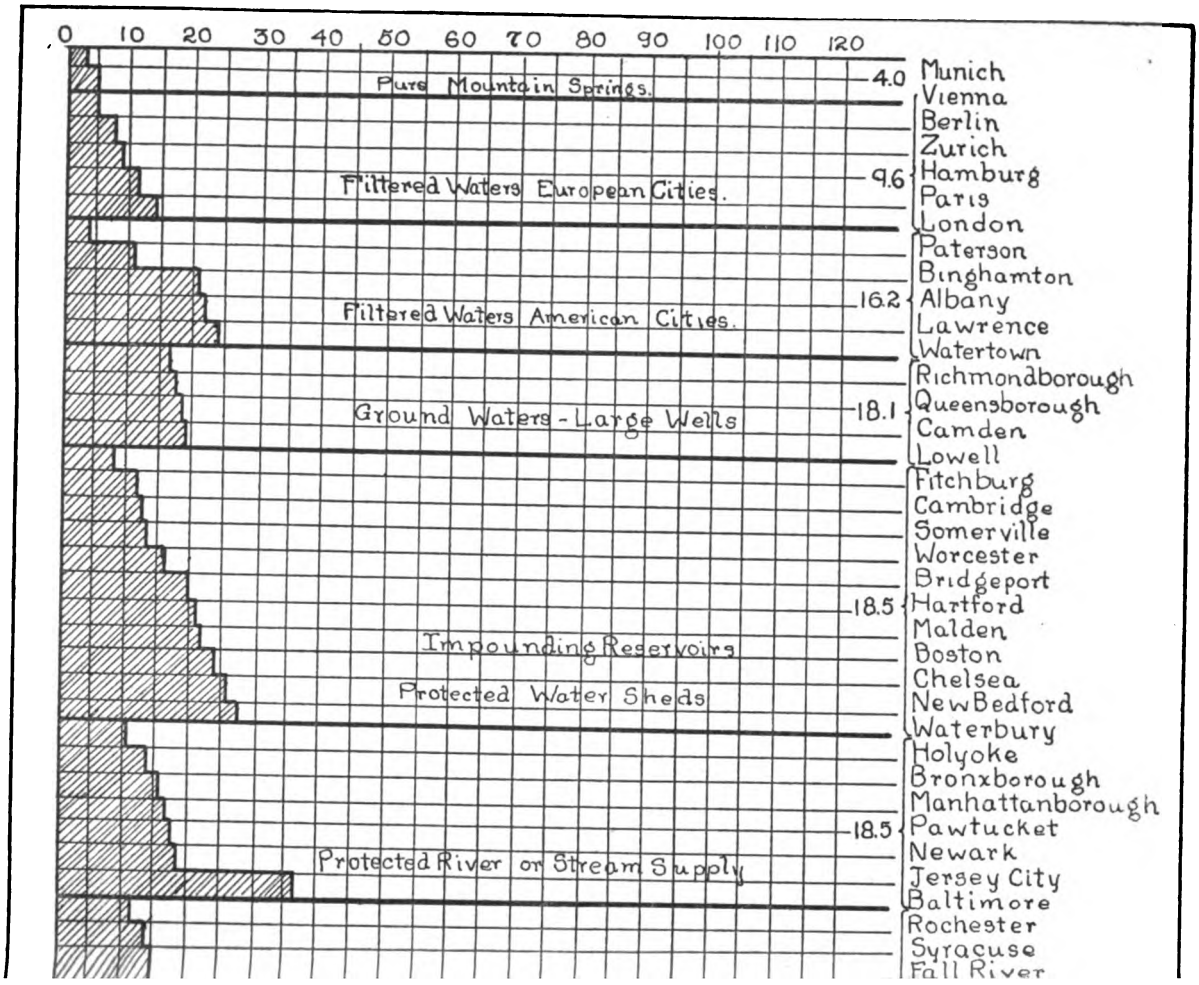
COMPARATIVE MORTALITY STATISTICS IN THE MUNICH GARRISON AS COMPARED WITH CITY MORTALITY (FROM SEITZ)

	City	*Garrison*
1855–1869	204	840
1876–1881	57	190

The great menace which typhoid fever has always been to armies, both in peace and war, is a matter which will be considered separately at a later point.

We are concerned at this point not so much with this interesting and striking diminution in the mortality rate itself, as with the causes which underlie it. These causes are, first, the full recognition of water contamination from sewage as the source of transmission in typhoid, as had been pointed out some years before by Budd,[2] and the consequent introduction of pure and safeguarded water supplies. And, second, the re-emphasis and rendering concrete of this first fact when transmission of the disease became typified in its recognized parasitic cause. The recognition of the etiologic importance of a specific bacillus of typhoid fever not only gave greater impetus in protecting water supplies from the dejecta of typhoid patients, but led undoubtedly to greater circumspection in handling the patients themselves and a consequent diminution in contact infections.

We may now consider in more detail the direct effect of the purification of water supplies on the mortality incidence of typhoid fever, particularly as it occurs in cities. This may be shown in two different ways: first, by comparing the incidence of the disease as it occurs in cities grouped in accordance with the purity of their water supplies; secondly, by comparing the incidence of the disease in any given city before and after any marked improvement in the water supply (Kober).


0 10 20 30 40 50 60 70 80 90 100 110 120
Pure Mountain Springs.
Filtered Waters European Cities.
Filtered Waters American Cities.
Ground Waters - Large Wells
Impounding Reservoirs
Protected Water Sheds
Protected River or Stream Supply
4.0
9.6
16.2
18.1
18.5
18.5
Munich
Vienna
Berlin
Zurich
Hamburg
Paris
London
Paterson
Binghamton
Albany
Lawrence
Watertown
Richmondborough
Queensborough
Camden
Lowell
Fitchburg
Cambridge
Somerville
Worcester
Bridgeport
Hartford
Malden
Boston
Chelsea
New Bedford
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Bronxborough
Manhattanborough
Pawtucket
Newark
Jersey City
Baltimore
Rochester
Syracuse
Fall River

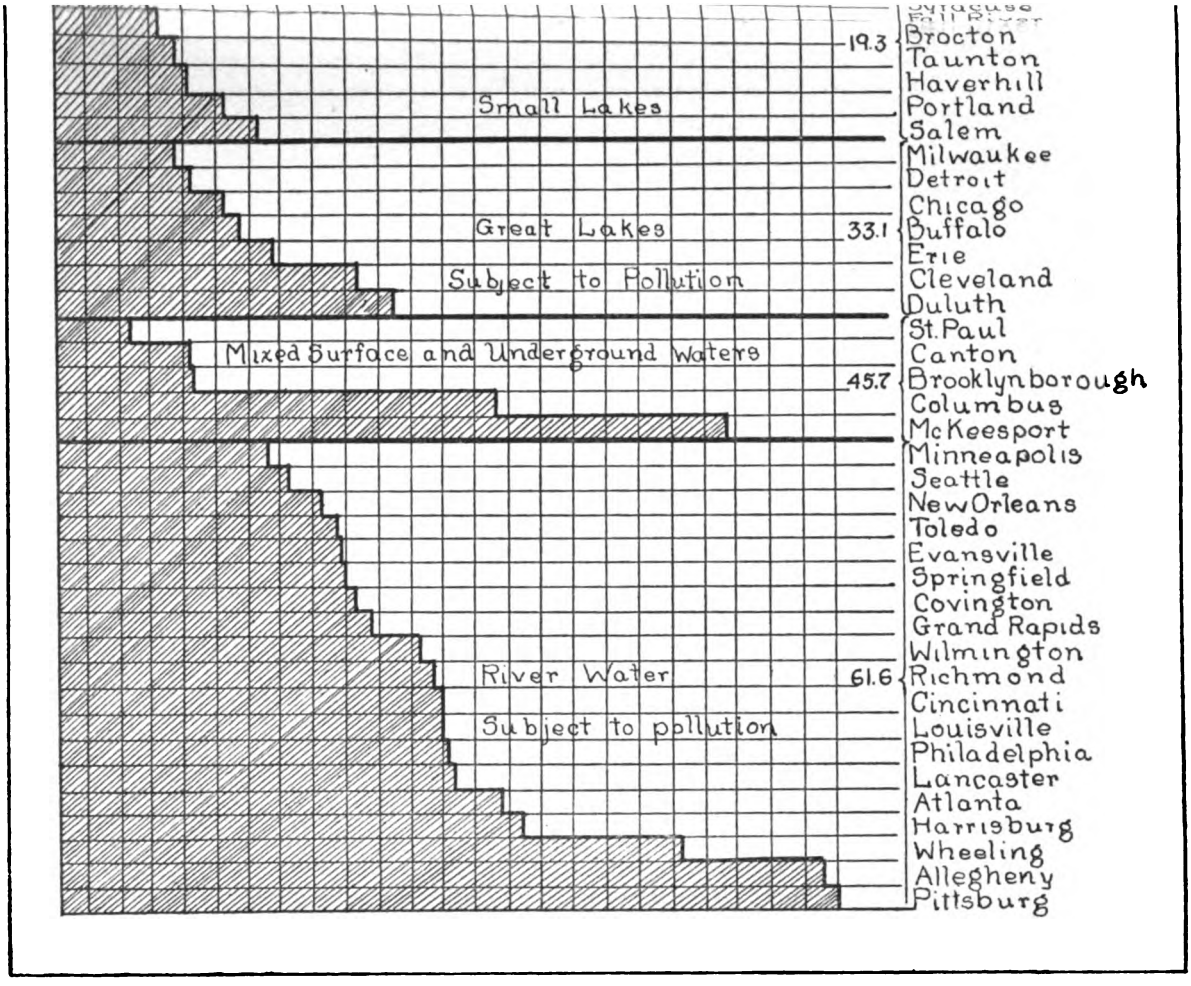

FIG. 1

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These two graphic illustrations show clearly the relation of purity in water supply to the incidence of typhoid fever. It is evident first (Fig. 1) that the purer the water supply in cities the less the incidence of the disease. In Fig. 2 it is shown that a change from a contaminated to a purer water source in any given city decreases the mortality at once. Owing to the close relation that exists between water supply and typhoid, the disease has been referred to by Sedgwick as a correct "sanitary index" of purity of water and food supplies.

We have seen, then, that typhoid fever was formerly a disease of crowded communities, occurring with greater frequency in cities than in the country, in crowded than in less crowded communities, and we have seen that a diminution in the mortality from this disease takes place in direct relation to the purity or the purification of water supplies. We may now consider more recent figures in reference to the occurrence of the disease in the large cities of Europe and of the United States.

TABLE III

COMPARATIVE MORTALITY STATISTICS OF TYPHOID FEVER IN CITIES OF CONTINENTAL EUROPE AND UNITED STATES

	Population	*Mortality Average*
33 largest European cities	31,500,000	1901–1910– 6.5
57 largest American cities	21,000,000	1910–19.59

In the first line of Table 3 is given the mortality average of typhoid fever during the decennial period from 1901 to 1910 in the thirty-three largest European cities with an aggregate population of 31,500,000. It is seen that the average mortality is extremely low, namely, 6.5 per 100,000 of population, and it is the more surprising when we consider that cities like Stockholm, the average of which is 1.7 for this period, are placed in the table, and also such cities as St. Petersburg, which has a mortality of 33.7 per 100,000 owing to the drinking of contaminated river water in the city.

It is interesting to compare with these European figures those for fifty-seven of the largest American cities with an aggregate population of 21,000,000. It is seen here that not only does the mortality exceed that of European cities by more than three times, but the figure for the American cities is taken at their very best, namely, at the last year of this period.

A further consideration of the American figures in still more recent years will be of interest at this point. In Table IV are considered the mortality statistics of typhoid fever in, first, the

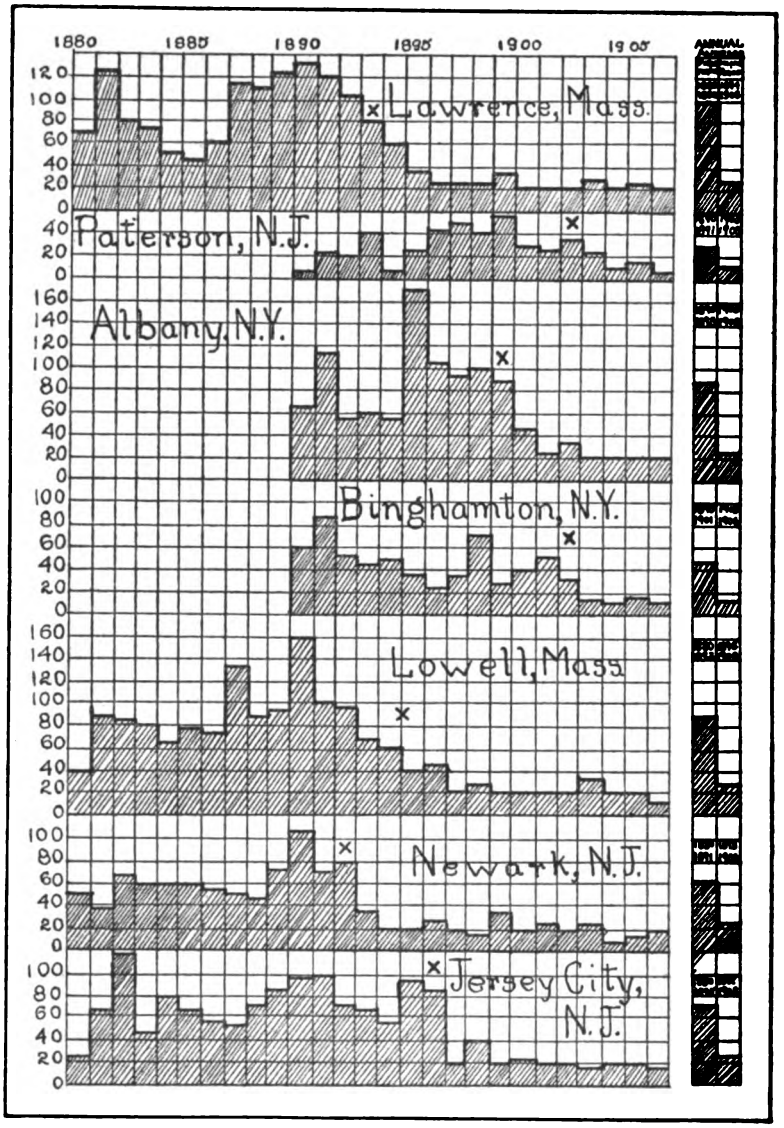
1880
1885
1890
1895
1900
1905
ANNUAL
Lawrence, Mass.
Paterson, N.J.
Albany, N.Y.
Binghamton, N.Y.
Lowell, Mass
Newark, N.J.
Jersey City, N.J.

Fig. 2

fifty-seven largest cities of the United States; second, the total registration area of the United States, which comprises twenty-seven states and approximately two-thirds of the total population; and, third, the figures in the United States army.

TABLE IV

INCIDENCE OF TYPHOID IN 57 CITIES OF THE UNITED STATES COMPARED WITH TOTAL REGISTRATION AREA AND THE UNITED STATES ARMY

	Cities	*Reg. Area*	*U. S. Army* *
1900–1904	——	33.8	—
1909	——	21.1	28
1910	19.59	23.5	16
1911	15.74	21	11
1912	12.56	16.5	3
1913	12.77	17.9	—

This table shows not only a gradual diminution in the death incidence in all three categories considered, but, what is more interesting, shows a complete reversal of form in relation to the disease incidence in rural and city communities that we have presented as characteristic in European cities in an earlier period. This change is chronological and not local, for whereas formerly the disease was primarily one of crowded communities, it is found now to be a disease of rural communities. Fulton has shown, indeed, that in five states of which the urban population was sixty per cent of the total, the average death rate of typhoid was twenty-five per 100,000, whereas in twelve states with an urban population which reached only ten per cent of the total, the average death rate was sixty-seven per 100,000. This change in typhoid mortality as between city and country is concretely illustrated in the Report of the New York State Department of Health for 1914, which graphically contrasts the mortality in New York City with that of the rural community of New York State as shown in Figure 3.

This figure shows a marked and nearly unbroken decrease in the city death rate between 1900 and 1914 of from 20.6 to 14 per 100,000, whereas the rural figures have remained stationary during the same period and have thereby come to exceed the city rate. This reversal of figures, however, is equally attributable to the same basis as the previous ones, namely, a purification of water supplies, because sewage disposal and water purification are now far better safeguarded in cities than they are in the country.

* Russell: [1] The sharp diminution in the U. S. army in 1912 is due to the introduction of vaccination in this year.

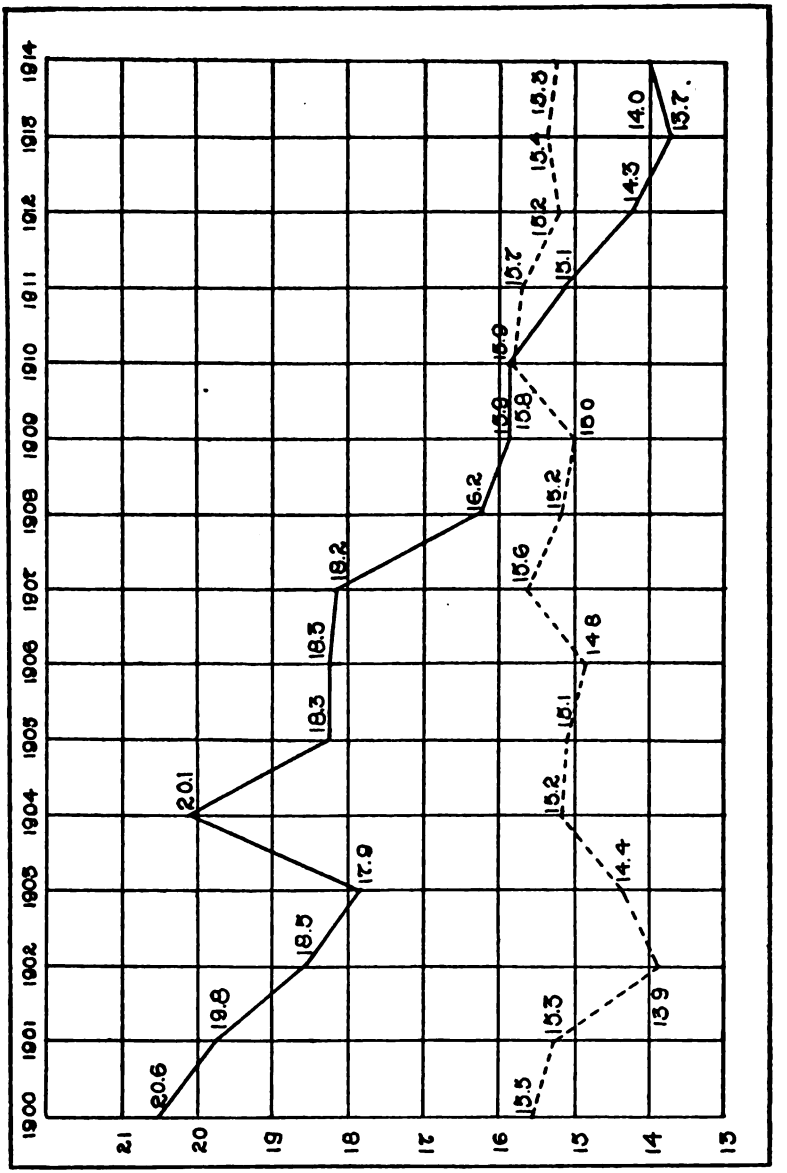

Fig. 3

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TYPHOID FEVER IN ARMIES

Appalling as has been the death rate from typhoid fever in civil communities, particularly in large cities, it was still greater in armies, as has already been indicated in Table II, and here again the same rule holds, the greater the density of the population the greater the incidence of the disease, owing in part to the contamination of the water supply; and, conversely, with purification of water supplies, the diminution in crowded and congested districts becomes rapidly less. Of almost equal significance in armies, prisons and asylums is the contamination of common food supplies by flies and human carriers, both matters which we shall consider in their proper place. In Table V we consider further mortality statistics from the Munich garrison over a period of years bearing obvious relation to a purifying of the water supply, which took place in 1880.

TABLE V

REDUCTION OF TYPHOID MORTALITY IN MUNICH GARRISON

1851–1860	1110	per 100,000
1861–1870	567	" "
1871–1880	466	" "
1881–1890	19.8	" "

The figures for the entire French and German armies during a similar period, not including the years during which the army was engaged in actual warfare, show similar results. Glenard has shown that from 1875 to 1880 there was an annual morbidity from typhoid in the French army of 380 to the 100,000. In the French army during this period typhoid fever was the cause of thirty-six per cent of all the deaths that occurred. No attention was paid to hygiene and water filtration in the French army until the year 1888, at which time it was estimated by the Minister of War, de Freycinet, that a reduction of thirty-six per cent in the number of cases took place in a single year as compared with the three previous years, and in the following year the reduction was forty-nine per cent. As indicating the extremes following sanitation, Kossel [1] mentions that typhoid in the German army produced a death rate in 1869 of 170 to 100,000; in 1909–1910 it had fallen to eight.

The figures for typhoid in armies under conditions of actual warfare are still more astonishing and have frequently been quoted. For example, during the American Civil War there are estimated

to have been 75,361 cases of this disease with 27,056 deaths. In the Franco-Prussian War there were 73,396 cases with 8,786 deaths, the latter supplying sixty per cent of the total mortality during this period. Even in recent times similar disgraceful figures have occurred, owing to the carelessness in camp hygiene and to the difficulty of securing a constant pure water supply. During our Spanish-American War in a force of 107,973 troops there were 20,738 cases of the disease with 1,580 deaths, constituting eighty-six per cent of all who died of disease (Whipple). These cases occurred peculiarly in camps that were more or less permanent and in the concentration camps, and one man in every five enlisted contracted typhoid fever. In the South African War in a force of 557,653 officers and men there were 57,686 cases with 8,225 deaths, whereas during the same war the deaths from wounds were only 7,582. The fact that armies are composed for the most part of healthy men of the exact age period which shows greatest susceptibility to typhoid is another contributing cause to the high army morbidity.

THE PRESENT ECONOMIC LOSS FROM TYPHOID

It is evident, then, from these summarized statistics that typhoid fever has been a disease of appalling frequency, the frequency until recent years varying directly with the density of the population and being due in large part to contamination of the water supply. With purification of the water supply and proper sanitation the mortality and morbidity from this disease have been remarkably diminished. In America, however, we have been extremely backward in proper appreciation of this menace and of the relative ease with which it can be checked, but even in Europe where greater precautions have been taken for a longer period of time, it has not been possible, particularly in the rural districts where typhoid fever is now more prominent, entirely to obliterate it.

This residuum of cases, particularly in the rural communities, is now found to be referable not so much to failure rigidly to safeguard water supplies as to other methods of transmission of the disease. After removing the large group of water contamination cases, which formerly monopolized the attention, it has become evident that another considerable number are due to contact infection, particularly through carriers. Vigorous efforts have been made in Germany to particularize and to obliterate these sources of infection. But these and other methods of infection as well

as more recent measures of prevention, as through vaccination, can more logically be considered in other connections.

Let us consider finally just what the significance of typhoid fever is in the United States at the present time and what economic loss it entails.

In 1900, there were in our country approximately 350,000 cases of typhoid fever, as has already been mentioned, and the cost to the community of this number of cases has been estimated by Whipple to have been something like $212,000,000. Whipple found this surprising total by evaluating an adult life at $4,634, which, with the total cost through disability for those cases that did not die, bring the total for each death to a loss to the community of something like $6,000. In a more recent estimate of the cost of typhoid fever in epidemics in Pittsburgh, which recurred for several years and mostly among the poorer classes, Wing has computed the value of each death to the community at something like $4,000, which he states is a very moderate estimate. The cost of each case for loss of wages, treatment, and nursing is in addition $128. On this basis the 198,000 cases (Dublin) which occurred in the United States in 1914, and the corresponding 19,800 deaths would have cost the United States for that year $104,544,000.

Another feature of typhoid fever in addition to the actual deaths that occur during the course of the disease is the lessened resistance for a certain period of time in those individuals that recover. Dublin has recently estimated that the incidence of mortality in typhoid recovered cases for the subsequent three years is over twice that among normal individuals. If the normal expectation of death for each of these three years is taken as one hundred, the expectation in typhoid convalescents is two hundred and four. On the basis of the typhoid incidence and deaths in 1914, as already computed by him, there must have been 178,200 recovered cases, and the extra deaths in these individuals attributable to the antecedent typhoid was 7,781. This would raise the national bill for this largely preventable malady for a single and recent year (1914) to $135,678,000.

The mortality danger in typhoid comprises not only those deaths due to primary typhoid infection or toxemia per se, but an even larger number due to the accidents and complications of the disease. Dopfer estimates that over seventy-five per cent of the fatalities are due to such causes. This tendency to complications, which is one of the characteristic features of the malady, in addition to their potential danger, adds still further to the dis-

tress, prolonged disability and cost to the individual. It would be impossible to estimate in what per cent of cases one or more of these complications occur. The percentage of deaths due to complications and also the percentage of cases in which each complication occurs, have both been estimated repeatedly. If we add together the percentage of occurrence of each of the major complications we find that several accepted lists will total over thirty per cent. This total is given with all reserve as to its actual significance, but is indicative of the frequency with which such untoward results occur in typhoid fever.

No attempt to indicate the severity of typhoid fever would be complete without some reference to the long duration of the disease itself. Apart from any complications or sequels, the fever itself lasts in even the mildest cases on an average of twenty-one days or more, extending in many of them to over thirty-three days (Curschmann). In McCrae's 1,500 cases the general average of the febrile period was 29.4 days and the actual period during which the patient was hospitalized was forty-nine days.

CHAPTER III

THE TYPHOID BACILLUS

BACILLUS TYPHOSUS AS THE CAUSE OF TYPHOID FEVER

The typhoid bacillus (Bacillus typhosus), first described in the organs of cases dead of typhoid fever by Klebs, by Eberth, and by Koch (1880), and first grown in pure culture by Gaffky (1884), may now be unreservedly accepted as the certain and single cause of the disease from which it derives its name. It may be obtained from the rose spots, circulating blood, stools, and urine during life, and from the characteristically affected organs after death in all cases of typhoid. It may be grown in pure culture and differentiated from similar organisms by means of appropriate media. The blood serum of cases of typhoid fever has the specific property of clumping typhoid bacilli, which property is not possessed by normal sera or sera from those suffering from other diseases. Typhoid serum exerts no effect on other bacteria, thereby further proving a causative relation between the bacillus and the disease. The typhoid bacillus is never found in normal individuals or in other diseases, except in a few recovered cases and in those rare instances of healthy carriers who, though themselves unaffected by the disease, may harbor the organism and transmit it to others.

It may further be shown that B. typhosus is the cause of typhoid fever in those cases which have followed accidental or intentional ingestion of pure cultures of the microorganism, and, finally, typhoid fever has been reproduced in all essential particulars in chimpanzees by feeding them with food containing a generous admixture of typhoid cultures or by smearing their mouths with such growths. These latter experiments, which we owe to Metschnikoff and Besredka,[1] and to which we shall refer in more detail in another place (Chapter V), showed, moreover, that it is in reality the typhoid bacillus itself and not some adherent filtrable virus that produces this characteristic malady.

THE CULTURAL CHARACTERISTICS OF BACILLUS TYPHOSUS

We may proceed, then, to the consideration of the characteristics of the microorganism. The typhoid bacillus has been

studied extensively, not only as the cause of a very important disease, but because it is difficult to differentiate from similar pathogenic bacteria and particularly from the colon bacillus, which is the normal and predominating inhabitant of the intestinal canal.

The typhoid bacillus stains readily either in tissues or in culture preparations with the ordinary aniline dyes. It is decolorized by Gram's method. It appears as a short, plump rod, varying in length from one to three microns and in thickness from 0.5 to 0.8 microns, being somewhat longer in fluid than on solid media. In old gelatine and potato cultures it may grow in chains or filaments of considerable length. In recent cultures the stain is absorbed uniformly, but in old cultures the protoplasm may stain somewhat irregularly.

The bacillus is usually actively motile in young bouillon cultures, particularly in dextrose bouillon or when suspended from fresh cultures on solid media; the motility may, however, be temporarily lost in old cultures or when the medium is too alkaline. The colon bacillus is less characteristically motile than Bacillus typhosus. The flagella which are present in both organisms also differ in their distribution and number. In Bacillus typhosus the flagella are arranged peritrichously and are eight to twelve in number, and measure six to eight microns in length; in Bacillus coli they are grouped at the ends and are usually only two or four, but may be more in the more motile strains. The typhoid bacillus does not produce spores.

Capsules have recently been described surrounding the typhoid bacillus by Kuhnemann and by Carpano. We have readily succeeded in repeating their results in various strains of the organism grown on different media (Gay and Claypole [2]). The clear zones which surround the bacteria when properly stained would seem, moreover, to be an actual part of the bacterial body and not artefacts, as judged from the careful studies of Marassini and Shimidsu.

Typhoid bacilli, when obtained from uncontaminated sources in cases of typhoid fever, or when derived from pure cultures, disseminated and poured in fluid agar or gelatine, grow readily and in a characteristic manner. On agar the surface colonies are thin, nearly transparent, and filmy; on magnification they are finely granular in appearance, are crenated and have well defined margins. Deeper colonies are lenticular or spherical and opaque. In gelatine the growth is naturally slower, the deep colonies are yellowish-brown in color and resemble those of Bacillus coli. On the surface they are bluish-white and leaf-like in character. The

colon colonies are larger in general than typhoid colonies. The typhoid bacillus does not liquefy gelatine.

In common with other members of the colon-typhoid group the typhoid bacillus grows readily in ordinary culture media but less actively than Bacillus coli. It flourishes best at body temperature, but will grow in a range roughly of from 8°C. to 43 or 44°C. It grows both aerobically and anaerobically. A temperature of 60° for ten to twenty minutes or of 100° for three minutes will kill the bacillus, but the resistance is greater when the bacilli are cloaked in such organic matter as feces. The majority of organisms when added to drinking water die in a few days whereas they multiply rapidly in milk. The typhoid bacillus will withstand low temperatures for a time, and even freezing, but tends to disappear rapidly in ice, nearly all the organisms being dead at the end of two weeks (Park and Williams). Typhoid bacilli are somewhat more susceptible to disinfectants than colon bacilli.

In bouillon Bacillus typhosus grows readily and uniformly and almost always without forming a pellicle, which, however, may occur when the medium is sufficiently alkaline. On agar and gelatine the growth of the organism is not distinctive, and similar to if somewhat less profuse than the colon bacillus.

Under proper conditions the growth of Bacillus typhosus on potato is differential from B. coli; in younger potatoes, where the reaction is acid, the growth of the typhoid bacillus is nearly invisible. The colon bacillus is cream colored or brownish and obvious; in older alkaline potatoes this distinction between the two cultures is lost, but the original conditions may be restored by adding a small amount of organic acid. According to Vincent and Muratet, whose statement we have readily confirmed, Bacillus coli rapidly produces a green color when grown on artichokes, whereas the typhoid bacillus does not.

The growth of Bacillus typhosus in litmus milk is characteristic and marked by little chemical change. In most instances a slight acidity is produced which is permanent, although in a few instances strains of typhoid may produce an initial acidity followed by return to an alkaline reaction which remains permanent. The milk is not curdled. In sharp distinction, Bacillus coli produces marked acidity and rapid coagulation of the milk. The acidity produced by Bacillus typhosus in milk is equivalent to less than three per cent of one-tenth normal acid, whereas that produced by Bacillus coli is seven per cent or more. In the case of the typhoid bacillus the acid comes from the small amount of dextrose and not from the lactose of the milk.

Bacillus typhosus in contradistinction to Bacillus coli does not produce indol in peptone water solution. It may, however, under artificial conditions of growth in rich peptone media be trained to do so.

According to Kendall, the typhoid bacillus liberates ammonia from protein in sugar-free media and also forms small amounts of non-soluble alkaline products as well. The reaction therefore becomes alkaline. When sugar is present the reaction is acid, owing to its fermentation, and the protein is not attacked. The acids formed are chiefly lactic acid with small amounts of formic acid. Most important in the identification of Bacillus typhosus and particularly in its differentiation from Bacillus coli and from intermediate organisms are the sugar reactions. In contradistinction to the colon bacillus, Bacillus typhosus does not produce gas in any of the sugar media and produces acid in fewer of the sugars than coli; acid is produced in dextrose, levulose, galactose, mannite and dextrin, but not in lactose and saccharose and dulcite, although in the latter acid may appear after several weeks.

BIOLOGICAL PECULIARITIES WHICH SERVE TO DIFFERENTIATE THE TYPHOID BACILLUS FROM OTHER BACTERIA

A very large number of methods and media have been devised for separating the colon-typhoid group of microorganisms from other bacteria, and still more for the purpose of rapid differentiation between typhoid, paratyphoid and other pathogenic members of the group and the colon bacillus. The latter, of course, are in particular designed to detect typhoid bacilli in the feces. These special methods are of great practical importance in the diagnosis of typhoid fever, in the detection of typhoid carriers and in the isolation of the typhoid bacillus from contaminated water, milk and food supplies. We shall discuss certain of these methods in more detail in those chapters which deal with the laboratory diagnosis of typhoid, the carrier condition and the differential diagnosis of the paratyphoid infections. We are concerned here not so much with the methods employed in diagnostic work as with the media and reactions employed as throwing light on the biological characteristics of Bacillus typhosus.

The in general superior motility of the typhoid bacillus has led to several methods designed to make use of this property in its separation from Bacillus coli. The semi-solid glucose gelatine-agar medium of Hiss serves in this way to differentiate colon from typhoid, since the latter on plating grow with peripheral, thread-like outgrowths into the media.

Carnot and Weil-Hallé [1] have made use of a "U" tube partially filled with sand through which the typhoid bacillus in a mixed culture will penetrate more rapidly into a bouillon medium stained with neutral red on the further side. The more rapid passage of Bacillus typhosus through filter paper and up into a fluid medium is employed by Wilman, who takes cultures at intervals and finds that the typhoid bacilli predominate at first even when more colon bacilli are present on the filter.

Various methods have been employed to suppress or inhibit the growth of organisms other than those of the colon-typhoid group by employing substances which leave the latter relatively unaffected. The cruder methods such as heat and the addition of carbolic acid have long since been abandoned. Various media for this purpose have included iodine, as in Elsner's potato gelatine. Bile is commonly used, particularly in blood cultures, as offering a favorable medium for colon and typhoid but inhibiting cocci and diminishing the bactericidal property of the blood. Crystal violet is also used to accomplish the first of these purposes.

Of even greater interest and importance are those chemicals which serve to differentiate between Bacillus coli and Bacillus typhosus by inhibiting the former. There are several important dye stuffs in this category, among which the most notable are malachite green, first employed by Loeffler and further perfected by Leuchs, and brilliant green employed in conjunction with picric acid by Conradi.[3] Malachite green has also been used in conjunction with bile. Both these substances inhibit the growth of colon bacilli and may be used either as a preliminary step in detecting typhoid bacilli or combined with other differential media. The value of both media has been repeatedly confirmed and details in their preparation and use modified in many ways. The addition of caffein to suppress Bacillus coli was first suggested by Roth and by Gæthens, and its value repeatedly re-asserted.

An apparently very successful method of killing the colon bacilli and leaving typhoids and paratyphoids unaffected has recently been described by Bierast.[1, 2] He finds that petroleum ether will produce this effect if a preparation with the correct boiling point (about 50° C.) is employed. Bierast's results have been fully confirmed by Jaffe and by Hall.[1, 2] Actinic light has been employed by Dreyer, Walker and Gibson [1] for the same purpose. An exposure of agar plates seeded with mixed cultures to a graduated arc formed between silver electrods leads to sharp differentiation in appearance between the colon and typhoid colonies.

Another group of diagnostic tests makes use of the greater fermenting properties of the colon bacillus in sugars, particularly in lactose, which is unchanged by Bacillus typhosus. Capaldi and Proskauer prepared two media containing mannite and litmus, only one of which contained peptone. In the peptone-free medium Bacillus coli grows well and produces acid, Bacillus typhosus giving no change. In the peptone medium both grow but the typhoid bacillus alone produces acid. Several indicators have been employed in detecting acid formation. One of the best known media is the lactose-litmus-nutrose medium of Drigalski and Conradi. Typhoid colonies appear bluish, whereas colon colonies are red on this medium; the red color is probably due to lactic acid formation (Robinson and Rettger) and not to aldehydes, as has been claimed. This medium is frequently used in combination with crystal violet to inhibit growth of other bacteria. Endo's lactose-basic fuchsin-sodium sulphite agar is even more favorably known. Colon colonies turn red and typhoid colonies are colorless or pinkish. Russell [2] renders the final differentiation of typhoid from alkali producers rapid and certain by transferring colorless colonies from the Endo medium to a double sugar medium prepared either in tubes with a solid bottom of glucose litmus agar, above which is slanted sterile lactose litmus agar, or by a mixture of the two sugars. The tube is inoculated by a combined stroke and stab culture which gives a blue background on the slant but a red glucose stab when the transplanted colony is the typhoid bacillus.

Another indicator which has been used in conjunction with lactose is congo red (Schmitz,[1] Liebermann and Acel [1]). Colon colonies are blue black and other bacteria red.

Holt-Harris and Teague have employed an agar containing saccharose and lactose, to which is added as an indicator a mixture of yellowish eosin and methylin blue. The colon colonies on this medium are differentiated earlier than on the Endo plate, and have distinctive black centers. The typhoid colonies are transparent and remain so. This medium in our experience is a very good one and can be successfully employed even in the hands of beginners.

Colon bacilli have a reducing action on certain media which is not shared by the typhoid bacillus. McConkey used an admixture of sodium glycocolate which is precipitated by the acid formed by Bacillus coli; he later added lactose and neutral red to this medium. Typhoid produces no change in either medium. Neutral red was suggested by Rothberger as a differential medium in stab

cultures. Bacillus typhosus produces no change in the red, whereas Bacillus coli decolorizes and renders the medium fluorescent. If glucose be added, gas is formed by the colon organism. Botez finds that typhoid will not affect bouillon colored with methyl violet, whereas paratyphoid A decolorizes it partially and paratyphoid B and colon reduce it entirely. Levy and Vallery-Radot have employed media containing subacetate of lead and glucose for the differentiation of typhoid bacilli from the two paratyphoid organisms. It is found that the typhoid bacillus does not break up the medium and may or may not darken it. Paratyphoid A on stabbing produces fragmentation of the medium without changing its color, whereas paratyphoid B both fragments and darkens it.

THE TOXINS OF BACILLUS TYPHOSUS

The typhoid bacillus produces symptoms and lesions in connection with the disease of which it is the cause, which are attributable to toxins rather than to its simple multiplication and parasitic existence in the body. The discovery of the soluble toxins of Bacillus diphtheriae and of Bacillus tetani about 1890 gave rise to studies of other microorganisms from the same viewpoint. Pfeiffer's studies of the cholera vibrio in 1892 showed, however, that filtrates of bouillon cultures of this organism differ from diphtheria culture filtrates in being slightly, if at all toxic for guinea pigs. His further experiments, in conjunction with Kolle, showed, however, that the dead bodies of killed vibrios were fatal even in small doses. When normal guinea pigs are given an intraperitoneal injection of living cholera vibrios, they die in twelve to twenty-four hours with increasingly evident symptoms, and cultures at autopsy show that the microorganisms have increased enormously throughout the body. In guinea pigs that have been immunized by repeated injections of small doses of killed cholera vibrios, a similar intraperitoneal injection of the dose of living vibrios which is fatal for the normal animal is followed by transitory acute symptoms of intoxication, rapid recovery of the animal and disappearance of the cholera vibrio. Further investigation showed that both the acute intoxication and the recovery of the immunized animal is due to the same cause. Specific lysins are formed as a result of immunization which may be shown both in the animal body and in the test tube (Metchnikoff) to dissolve the vibrios, which not only destroys them but liberates their intracellular poisons or "endotoxins." It is evident, then, that under the conditions of immunization

which Pfeiffer pursued, lytic bodies which destroy the vibrios were formed, but no antibodies capable of neutralizing their liberated endotoxins; he therefore defined endotoxins as bacterial products which differ from the soluble or exotoxins like those of Bacillus diphtheriae in residing only within the cell and in failing to give rise to antitoxins.

Such intracellular poisons or endotoxins are obtainable from the bodies of most or perhaps all bacteria which do not give rise to the soluble toxins of the diphtheria-tetanus class. They may, moreover, be derived not only from pathogenic but from non-pathogenic bacteria. Toxic extracts of this sort have been obtained from the typhoid bacillus in several ways: by employing old macerated cultures (Sanarelli, 1892–1894); by killing with chloroform and heating (Martin, 1898); by freezing with liquid air and grinding (MacFadyan and Rowland, 1903); by mixing with a solution of urea and freezing by methyl chloride (Balthazard); by drying and grinding with common salt (Besredka,[1] 1905); by crushing under four hundred atmospheres in a Buchner press ("Typhoplasmin" of Hahn, 1897); by autolysis (Conradi); or by splitting the microorganisms by alkali-alcohol (Vaughan, 1908). These extracts when injected into animals produce symptoms and lesions, which in some ways suggest relations to those of human typhoid fever, and which we shall consider in more detail presently. They cannot, however, be regarded as strictly specific in their action, as identical results may be produced with the extracts of other bacteria, for example, the colon bacillus. It may, however, be suggested that these experiments have not been carried out on anthropoid apes in whom alone the characteristic human syndrome has been produced with the living bacteria, and specificity could scarcely be expected from the toxic products in lower animals. The relation of this endotoxic product from the typhoid bacillus to the symptoms and lesions in typhoid fever we shall discuss in a later place; suffice it to say that the relation is by no means as simple a one as would appear, being complicated not only by the effect of a possible soluble toxin but also by the indefiniteness of our knowledge of the endotoxins themselves, and of the nature of bacterial anaphylatoxins.

Preceding the work of Pfeiffer and Kolle, on which the conception of endotoxins was founded, there had been observations that indicated that typhoid bacilli eliminate toxins into culture media during their growth. These observations date from the experiments of Brieger in 1883, thus antedating the actual growth of the typhoid bacillus in pure culture by a year. The observations,

however, are rendered doubtful by the uncertainty as to whether pure cultures were actually obtained, by the complicating factor of possible toxicity of the culture medium itself, and by the indefinite nature of the poisons that were actually obtained. The later observations of Bandi, 1889, of Chantemesse, 1897, and of Rodet, 1898, seem to prove, however, that a true soluble toxin may be formed under certain conditions by Bacillus typhosus. These observations were to a considerable extent discounted during the following ten years when the endotoxin idea of Pfeiffer dominated conceptions as to the type of poisons that are actually formed by the majority of bacteria, in contradistinction to the few active toxin producers like diphtheria. Recent work, however, in the hands of Aronson, Meyer and Bergell, Kraus and Stenitzer, and Yamanouchi would seem to have proved conclusively that exotoxins are produced by the typhoid bacillus if suitable conditions of medium and bacterial strain are chosen. These soluble toxins in no wise equal diphtheria or tetanus toxin in potency, but would seem to differ from them only in degree. Arima thinks that two different toxins are formed by Bacillus typhosus, an exo- and an endotoxin, which he is able to differentiate on the basis of certain chemical reactions and the lesions produced experimentally in animals. The major results following the intravenous injection of the exotoxin in proper doses are a rise in temperature, paralysis, anorexia and marasmus; coagulation necrosis and waxy degeneration of the heart muscle and kidneys, swelling and hemorrhage of the adrenals, parenchymatous degeneration of the liver, and, finally, diarrhea. The endotoxin, on the other hand, produces a characteristic lesion in the intestine which suggests human typhoid, characterized by hemorrhages into Peyer's patches. These lesions are accompanied by fever, anorexia and marasmus.

The production of soluble toxins by the typhoid bacillus is certainly less easily demonstrated than the presence of toxic substances lying within the bodies of the bacteria, and success in producing the former would seem to depend largely on the strain of bacillus employed and simple adjustments of the reaction of the culture medium. We cannot readily accept the sharp distinction which Arima would draw between the two toxins, which he has described, and it would seem to us more reasonable to assume that the difference between exotoxins and endotoxins lies, first, in the amount of toxin that is formed, and, secondly, in the ease with which the toxins are liberated from the body of any given bacteria rather than an essential difference in the toxic products themselves. Variations in these two criteria would depend on the

strain of culture employed and the suitableness of the medium in which it was grown. This lack of distinction between the two classes of toxins is further rendered probable by the fact that one of Pfeiffer's original criteria of endotoxins seems to have been disproved. Besredka has shown that the endotoxins of both cholera and typhoid can give rise to antibodies. These antiendotoxins are, to be sure, incapable of neutralizing any considerable number of toxin doses, but the point of interest here is that the typhoid antiendotoxin of Besredka will neutralize not only the endotoxin but also the exotoxin (Arima, Stenitzer).

Both Castellani [1] and Levy and Levy have found that filtrates of sugar-free broth cultures of typhoid bacilli are hemolytic. These hemotoxins on injection into animals give rise to antibodies. There is no indication, however, that they play any particular rôle in human typhoid fever.

MUTATIONS AND VARIATIONS IN BACILLUS TYPHOSUS

The question of mutation in bacteria is one of the most interesting problems with which the science of bacteriology has to deal. In no particular instance is it more concretely of interest than in the case of the typhoid bacillus. Whereas Naegeli's original conception of bacteria was that they were essentially variable in appearance and function as well as in their properties of producing disease, the work of Cohn and Koch, on which our present day classification and ideas of specificity are based, depends essentially on the immutability of bacterial species. It is obvious that the one essential qualification in proving that a given microorganism is the cause of any given disease, is that it should be an entity sufficiently fixed so as to make its identification certain. The studies of recent years, however, employing more delicate methods of cultural and immunological differentiation, have tended to show that whereas a given bacterial species remains fixed in its principal characteristics, it may tend to fluctuate and to be divisible into groups in some of its less important functions. It has been shown, for example, that although the pneumococcus is still a recognizable entity as the cause of acute lobar pneumonia, it may be subdivided into several types on the basis of agglutination tests, which types are correlated with distinct differences in respect to relative pathogenicity. There is also a tendency to divide the gonococci, the streptococci, and the meningococci into similar groups. In the case of bacillary dysentery it is generally recognized that there are at least three or four well marked types of bacilli, any one of

which may give rise to the characteristic disease. Not only do these different types occur in different cases in a given epidemic, but they may be shown to be present in a given case. It is evident, then, that considerable variation may occur in a given species of bacteria without producing marked effect, except in degree, on the essential pathogenic properties of that microorganism. The bacterium remains a recognizable and specific entity and the slight variations which we are beginning to recognize in members of a bacterial species may be produced experimentally only with the greatest difficulty or not at all. The Shiga and Flexner types of dysentery bacilli differ only in their response to immune sera and in the fermentation of certain sugars, and yet we cannot transform one variety into the other by any methods at present at our disposal.

In a more extended way we may imagine that the typhoid and paratyphoid bacilli were originally derived from the colon bacillus, with which they may still be grouped in general characteristics. The typhoid and the paratyphoid bacilli produce definite and very similar human diseases, the similarity becoming more evident as we have learned more about the paratyphoid fevers, and yet they are fixed types in the sense that we differentiate entirely on the basis of the variations in these microorganisms between the paratyphoid and typhoid fevers. There are groups of bacteria intermediate between the closer paratyphoid organism (Bacillus paratyphosus A) and the typhoid bacillus, and these variations or mutations may remain more or less constant. There are further mutations among the organisms that may definitely be classified as typhoid bacilli. These mutations consist, first, in variations from the normal type in the appearance of the colonies or in the individual organisms, and such forms may tend to remain constant in successive generations (Baerthelin). Other strains of typhoid bacilli isolated in epidemics which showed a predominance of the usual type have shown variations in respect to growth on the ordinary media. Jacobsen describes an organism to which he gives the name Bacillus typhus mutabile, which failed to grow on the Drigalski-Conradi medium, although other organisms in the same epidemic grew perfectly well. This mutant fermented mannite slowly and was only weakly agglutinated by an antityphoid serum; otherwise it grew like the regular strains of the organism. It finally became agglutinable and it could be shown that a slight change in the reaction of the medium led it to grow even shortly after its isolation.

Most interesting, however, are the induced variations in typhoid

bacilli that have been produced by several investigators. Twort by growth of an ordinary typhoid bacillus on two per cent lactose media for two years finally produced a strain which would ferment this sugar; this property remained constant even after passing the acquired strain through animals. Penfold studied this particular strain as regards its acid formation on McConkey's lactose bile neutral red agar, and found that whereas a given colony when grown and seeded would produce equal numbers of red and of mixed pink and white colonies in the first generation, the subsequent planting from a red colony would give ninety-five per cent of red colonies, and from a pink colony both pink, red and white colonies. When the organism was grown in bouillon that contained no lactose for five to twenty passages, it reverted to its original non-acid production, and all the colonies are white. Penfold was unable to produce similar mutants in a year from regular typhoid bacilli. He did, however, succeed in producing a strain that fermented dulcite in an increasingly shorter period of time. Mandelbaum has described a peculiar ("metatyphosus") form of organism which produces alkali in glycerine, although the ordinary typhoid bacillus produces acid. He could not produce a similar mutant artificially, but was able to reduce the alkali form to the regular acid production in a number of generations.

These variations in the metabolic activities of the typhoid bacillus, interesting as they are in proving the existence of mutants, are of less importance from the standpoint of the pathogenicity of the organism than are similar variations in the so-called antigenic properties of the bacillus. There is observational evidence which would seem to show that there is variation in the pathogenicity of different strains of the typhoid bacillus. It must be admitted that this evidence rests on no very secure foundation inasmuch as it cannot be experimentally verified, but it would seem evident, apart from the variation in resistance in individuals, that there is an actual variation in the severity of different epidemics, and indeed in individual cases in a given epidemic, which seems to indicate that the infection in various cases may vary apart from the matter of dosage and the like. As we have stated, these matters are not subject to experimental investigation, although it has been the practice in what would seem to be a thoughtless and arbitrary fashion to judge of the pathogenicity of a given bacterium isolated from a human case by injecting it into animals. This procedure, which has grown up as a sacred rite in many pathological laboratories, would seem devoid of any intelligent purpose. The mere fact that a given strain of microorganism may

produce a more severe disease in rabbits than other similar strains of the same organism gives us no certainty that it will produce similar results in any other animal species. There is no reason, then, to draw any conclusions from the effect of a given bacterium isolated from a human case by observing its relative pathogenicity for animals.

The matter of variations in pathogenicity is, however, of great importance when we consider the question of specific immunization, be it active or passive in type. There is ample evidence to show that the best type of active immunization or vaccination against a given microorganism is obtained by immunising with the particular strain of microorganism against which protection is desired. This has been amply shown, particularly in the case of the streptococcus. We shall not enter at this point upon a discussion relative to the value of a single (monovalent) or of a polyvalent typhoid vaccine as giving protection against typhoid fever. That matter will be considered more particularly under the discussion of protective vaccination against this disease. We do wish, however, to point out not only that variations occur in the antigenic properties of typhoid bacilli as they are isolated, but that they may be artificially induced in them. It is first of all well recognized that recently isolated strains of typhoid bacilli are not infrequently difficult to recognize on account of their failure to produce the characteristic reaction to an antityphoid diagnostic serum. This relative inagglutinability corresponds, we believe, to a growth in the body on a different type of medium than the one ordinarily used to grow bacteria outside the body, and the inagglutinability may be induced, as Gay and Claypole have shown, by growing the typhoid bacillus on a blood medium. Typhoid bacilli vary in their property of producing soluble toxins, according to Kraus and Stenitzer. An artificial resistance of typhoid bacilli may be produced not only to chemical substances, as indicated by the references we have given on the variation in fermenting properties, and further work which has shown that the organisms may be made relatively resistant to a substance such as quinine by successive growth in this medium (Haendel and Baerthlein), but also to serum. Braun and Feiler, and Neufeld and Lindermann have both shown that growing typhoid bacilli in normal or in immune serum may make them relatively resistant to destruction by the serum in question. The general experience that the presence of fixation antibodies in the serum of typhoid cases can only be detected to best advantage by the use of a polyvalent antigen is best indication that variations occur in the in-

dividual organisms that may cause the infection in any given case.

It has recently become evident that not only may variations in the antigenic properties of typhoid bacilli occur and be artificially induced, but that such variations may to some extent serve to classify the strains into groups. Hooker in a very careful study of the antigenic properties of strains of typhoid bacilli has found that consistent differences may be detected by means of very delicately adjusted alexin fixation reactions or by means of agglutinin absorption experiments. He was able to divide the typhoid bacilli which he studied into three groups of this sort. His observations indicate not so much that the groups vary remarkably among themselves when recently isolated, but rather that old cultures of the organisms tend to lose certain antigenic properties, and his facts are applicable perhaps rather to the type of bacillus (a recent strain) which should be used in preparing vaccine for protection. There is, however, evidence at least from his agglutinin absorption experiments of distinct antigenic differences among recently isolated strains. Weiss has independently corroborated and extended these observations of Hooker. This writer found that he could divide the strains of typhoid bacilli which he studied into several groups, not only on the basis of agglutinin absorption experiments, but also by their ability to ferment xylose.

CHAPTER IV

THE MODES OF INFECTION IN TYPHOID FEVER

It will be recalled that one of the criteria by which Gerhardt and others were enabled finally to differentiate typhus from typhoid fever was the high degree of contagiousness, as they called it, or as we should now better say transmissibility, of the former and the supposed non-contagiousness of the latter. We find that the physicians of the early nineteenth century were practically unanimous in regarding typhoid fever as entirely non-contagious, but, as we shall see, this belief gradually changed with the subsequent observations which we shall endeavor here to trace. The French physicians, Chomel, Bretonneau, Louis and others, were the first accurately to describe typhoid fever on the basis of its characteristic lesions, although they did not have sufficient experience with typhus to be able to differentiate it from this latter disease.

TRANSMISSIBILITY OF TYPHOID FEVER AND GENERAL CONCEPTIONS OF ITS MODES OF INFECTION

According to Bartlett, Nathan Smith in 1824 was the first to refer to typhoid as transmissible from one individual to another. Inasmuch as the disease was not at that time clearly separated from typhus, no particular significance can be attached to this observation. It was undoubtedly Leuret in 1828 who proved that a series of cases of typhoid in Nancy, which were anatomically verified, could be traced to a stranger suffering with the disease who came to the city. In the following year (1829) Bretonneau gave further evidence on the transmissibility of the disease, which he was able to follow owing to the fact that the cases he observed occurred in the country, where for reasons that will later be mentioned the course of epidemics is more readily followed. In 1834, Gendron proved conclusively that in several instances a number of cases of typhoid occurred in a series following the introduction of an imported case, and made definite statements as to the probable method of its transmission. He concluded that the majority of cases arise through direct or indirect contact of healthy individuals with one sick of the disease, either through living in

the same atmosphere or indirectly by means of the clothing or utensils that have been handled by the patient. He further stated that epidemics of typhoid are the result and not the cause of the contagion. Contagion would apparently depend on the directness of communication between the individuals affected, and bears no relation to the sanitation of the locality in which the disease arises. Gendron, however, ingeniously points out that typhoid fever is more contagious at certain stages of its evolution and may be transmitted even by convalescents.

Dupré was apparently the first (1823) to mention the importance of water as a means of transmission of the disease (Brouardel and Thoinot). Austin Flint in 1843 records a memorable epidemic which occurred in North Boston, New York, in which a series of cases could be traced directly to those who had drunk of the water at an inn in which a traveler had fallen ill of typhoid.

The evidence in favor of the contagiousness of typhoid was summarized by Piedvache in 1849, who defined contagion in a manner that is particularly acceptable for typhoid fever in the following words: "Toute transmission de la maladie d'un individu malade à un individu sain quel que soit le mode suivant lequel elle s'opère." This author regards typhoid as contagious in at least the majority of cases, in which viewpoint he had been preceded by Louis in the second edition of his well known book on the disease.

The other important link in the chain of evidence which proved the transmission of typhoid fever from one individual to another, was the recognition that the "contagion" or vehicle of infection was from the sick to the healthy by means of the excreta. This was apparently first clearly stated by Canstatt in 1847. Riecke in 1850 apparently connected the two significant factors of excreta and water by showing that a number of epidemics could be directly traced to the ingestion of drinking water that had been polluted with sewage.

It remained, however, for William Budd to furnish complete and sequential proof of the successive steps in the usual mode of transmission of typhoid. In two remarkable articles published in the Lancet in November and December, 1856,[3, 4] he outlines his conception of the nature, mode of spreading and prevention of typhoid, which he further amplified in his book published in 1873.[2] Since the conception of this author represents the essential framework on which our present conception of the mode of transmission of this disease rests, it will be worth while to give his major conclusions in some detail. According to Budd, the living con-

tagion of typhoid fever inhabits the human body primarily, in which place alone it finds conditions suitable for its development. The disease which this contagion produces is transmitted more or less directly from one individual to another by means of the excretions and effluvia from the first affected person. The principal excretion responsible for the transmission is the feces, and sewage is to be regarded, in so far as the transmission of the disease is concerned, as simply a continuation of the intestinal canal. Ordinary sewage, uncontaminated by typhoid excreta, is not capable of causing typhoid fever, however much it may contaminate the water which is the usual vehicle by which it reaches the second person. Budd attributed his success in tracing the course of several epidemics to the fact that his observations were made in the country where sanitation is less perfect than in cities. Excreta were deposited upon the ground and could then be shown in a number of cases to be washed by rain or in other ways to reach water supplies, which gave rise to other cases. In other instances it was shown that the disease was transmitted from one to another by the hands coming in contact either with the sick individual or with fomites which had been soiled with the excreta from such an individual. Budd further mentions definite instances in which people were apparently able to give rise to epidemics even though they themselves had for some time been without fever and apparently restored to health, thus forestalling the important conception of recovered carriers which was not elaborated until many years later. He further points out that failure to succeed in tracing any case or epidemic to a preceding case of typhoid is a fallacious means of proving that such transmission has not in reality taken place. The English author was by no means satisfied with explaining typhoid epidemics, but took vigorous and successful means in preventing their further spread and recurrence by laying down thoroughly practical and successful methods of disinfection, which are as applicable today as when they were proposed.

Before passing to more modern and more detailed explanations of the entire question of typhoid transmission, we may mention two theories which were developed in the middle of the nineteenth century, although they in reality added little to Budd's theory, and indeed in some respects serve to obscure it. As we have already stated in the first chapter, Murchison contributed additional facts which prove the communicability of typhoid and its transmission through the feces, although his explanation was marred by the assumption that certain fermentative changes in

the feces of a typhoid case were necessary before the contagion was again capable of producing the disease. He further made the serious error of assuming that spontaneous generation of the disease was possible in sewage which had been uncontaminated by typhoid excreta. The ground-water theory of Buhl and Pettenkoffer is interesting only so far as the importance of water as a vehicle of transmission is indicated, but is wholly incorrect in again assuming the spontaneous origin of the disease.

The preceding sketch of the development of knowledge concerning the mode of transmission of typhoid fever, extending to the middle of the nineteenth century, may, when supplemented by the data introduced by bacteriology, be regarded as comprising the essential facts in our present day knowledge. All subsequent information, extended and elaborate as it is, has not supplanted the explanation of Budd, and has for practical purposes added little to it. The first fact of importance is that every case of typhoid fever arises directly or indirectly from some previous case. The first link in the chain which connects one case with another lies in the dejecta and objects that have been in contact with the first patient. Contaminated water is the most frequent vehicle by which the infection actually reaches the second individual. If all dejecta from the first case were destroyed and all direct contact were prevented or neutralized by cleanliness, typhoid fever would cease to exist. The disinfection of the feces is, as we now recognize and as Budd emphasized, the most logical and vulnerable point at which to interrupt this self-perpetuating malady.

SOURCES OF INFECTION FROM THE TYPHOID PATIENT

An exposition of the disease entity which we are considering may begin at any point in the continuous chain which stretches through one case of typhoid fever to the next victim. We have chosen to begin with a consideration of the parasitic essential agent of the disease, the typhoid bacillus. We have examined this microorganism as it may be studied under artificial conditions outside the human body. In the present chapter we are investigating the natural but still less favorable conditions under which it occurs "at large," and shall endeavor to trace it to its normal habitat in the body of man. In following the course of the typhoid bacillus from one host to another we may begin by a brief summary of the conditions under which it is present in the body, and its method of leaving it, forestalling in a way the full consideration of these phases which we take up later.

Any case of typhoid fever may serve as an immediate source of infection for healthy individuals, and all typhoid cases are in the last analysis derived from previous cases. Each individual case varies as a potential source for the further propagation of the disease in a degree which varies, depending on the number and virulence of bacteria eliminated. Each particular case, moreover, varies at different stages in its development in the number of bacteria excreted. A typhoid case may excrete bacteria at any time during its course, not only during the stage of active manifestations of the disease, but before and after this period. The course of the disease, moreover, includes the incubation period, during which the patient is apparently perfectly well, and although at this stage the number of bacteria is probably less, the actual dangerousness of the individual as a source of infection is probably greater, owing to the fact that no suspicion as yet attaches to him. This same absence of diagnosis renders infection quite common from cases in the first week of the fever. It has been estimated, for example, by Conradi that fifty-eight per cent of the cases in an epidemic which arose from a certain case were caused by the excretions during the first week. From the third week on typhoid bacilli may be found with greater regularity in the feces, in some seventy-five to eighty per cent of all cases. The actual detection of the organism, naturally, falls short of its actual occurrence in the feces, and from what we know of the course of the disease, we may assume that it is always present. Atypical cases of typhoid are particularly dangerous from the standpoint of hygiene, owing to the fact that their real condition is not appreciated. Among these may be mentioned the ambulatory and mild cases of typhoid, and particularly typhoid as it occurs in children, where it is frequently not correctly diagnosed.

Typhoid carriers are the source of many subsequent cases, and the proof of the existence of these individuals may be regarded as one of the triumphs of preventive medicine. The carrier, like the case of typhoid during the incubation period, is a great danger because unsuspected. Large epidemics, particularly food epidemics, may be directly referable to carriers, and they constitute a very important source of infection, although the estimates which are given as to the total percentage of cases caused by carriers vary considerably and depend, of course, on the individual experience of the author. Percentages ranging all the way from two to thirty have thus been attributed to carriers. Typhoid carriers may be divided into three categories: carriers in recovered typhoid cases, which are subdivided into temporary and per-

manent; and the healthy carriers. Whereas the typhoid bacilli disappear from the feces in the majority of cases during convalescence, they persist for a few days or weeks in four or five per cent of recoveries. In two per cent they persist for two or three months, and in something like one per cent they persist beyond this period. The latter individuals are the true permanent carriers. Healthy carriers are those individuals who have never, so far as is known, suffered from frank typhoid fever, but who nevertheless harbor the bacilli in their intestines. We shall later give reasons for assuming that these cases must in reality have passed through a mild attack of the disease, since it is probable that the excreted organisms come from the gall bladder after having passed through the body rather than from simple multiplication in the intestine. Carriers serve as sources of infection, particularly in those cases that are infected through contact, and most frequently in those in which the contact is indirect, as in the preparation and contamination of food. The percentage of women among the carriers is higher than men.

As we have already described, the means by which the typhoid bacillus leaves the body of the original case is primarily through the feces. As has been stated, the typhoid bacillus can actually be found in eighty per cent of cases in the feces, and is undoubtedly present in every case and probably in very large numbers. It tends, however, to disappear somewhat rapidly after excretion from the body in manners which we shall presently describe. The urine is the next most frequent route by which typhoid bacilli leave the body. Twenty-five per cent of all cases give positive cultures from the urine and most frequently during the third week of the disease. The bacilli are not only present during the disease, but, as in the case of the feces, may be present after recovery for varying and considerable lengths of time. It has been estimated that seven per cent of all permanent carriers are urinary and the majority of these are women. The typhoid bacillus occurs in the urine, particularly when it is alkaline. The danger of indiscriminate scattering of the bacilli has been pointed out to be somewhat greater from the urine than from the feces.

In addition to the feces and urine, which represent the major sources of the typhoid bacillus in the human body, there may be mentioned certain other excreta which at times not only contain typhoid bacilli but also may at least be assumed to give rise to further cases. Among them there may be mentioned the sputum, which, during the occurrence of typhoid ulcers in the throat or of typhoid bronchial pneumonia, has been shown to contain numbers

and often pure cultures of the specific bacillus. The vomitus during the early stage of the disease, particularly when bile-stained, contains typhoid bacilli. Certain of the localized complications of typhoid fever which occur not infrequently during or after convalescence, are due to the typhoid bacillus, which may be in pure culture or mixed with other organisms. Thus, otitis media and necrosis of the bone may occur for very long periods after the disease. Netter (Vincent and Muratet) has described a form of vulvitis in children produced by the typhoid bacillus which might readily serve as a source of infection.

THE TYPHOID BACILLUS AT LARGE

Typhoid bacilli under ordinary circumstances begin to diminish immediately on their discharge from the body of their host, and this fact serves as one of the safeguards in the distribution of the disease. Each successive link in the chain which connects the first typhoid case with the second would in general tend to diminish the danger of infection owing to this fact that the microorganisms are living in unfavorable surroundings. We shall discuss the conditions in each of these stages of transmission as we reach them, and may content ourselves here with certain observations as to the life of the typhoid bacillus in the feces. It is probable that the microorganisms in feces do not survive for any considerable period of time. Park has shown that the majority of organisms in his experiments survive only a few hours, although in some specimens they were present as long as fifteen days. It is probable that the reaction of the stools is of considerable importance in determining the longevity of the typhoid bacillus. Rosenau estimates that under ordinary conditions the organism survives for from two to seven days. Vincent and Muratet cite experiments which indicate that the duration is considerably longer, from twenty-five to thirty days, and Levy and Kayser found organisms in a cemented privy vault five months after their excretion. A number of factors intervene in determining the life of the typhoid bacillus, both in the feces and in other media, with which they become contaminated. Certain requisites are necessary for the life of the bacillus itself, the principal ones being food, the exact composition of which is not certain, moisture, and warmth. Among the harmful influences that tend to destroy the typhoid bacillus are sunlight and temperatures too far above or below that of the human body. Other factors which contribute in the destruction of the bacillus are antagonistic bacteria and, when

the feces are mixed with the general sewage, the absence of oxygen. It seems certain in general that the greater the general pollution, apart from the typhoid bacillus, the less the opportunity of the latter to grow. It seems fairly well demonstrated that the typhoid bacillus will live longer in clean water than in sewage. The typhoid bacillus may, however, persist even in the effluent from septic tanks.

ROUTES FOLLOWED BY THE TYPHOID BACILLUS FROM ONE INDIVIDUAL TO ANOTHER

The typhoid bacillus having left the body of the typhoid patient or carrier with the feces and urine, or perhaps in some instances with other excreta, may follow a more or less direct route in reaching the mouth and gastro-intestinal tract of its next victim. The various routes of transmission have been followed with varying accuracy and certainty in innumerable cases and epidemics, and increasing unanimity has been reached as to the more important ones. We might follow these routes and the vehicles of infection that constitute them in the order of their importance, but since estimates as to relative importance differ and the stages in the routes vary in number, it may be clearer to discuss the known or suspected paths in the order of their complexity.

Contact Infections in Typhoid

Routes 1-5

In recent years more and more emphasis has been laid on cases of typhoid due to contact, and contact, again, has been found to be direct or indirect. Accepting the excreta, in particular the feces, as the extra-corporeal source of typhoid bacilli, the contact cases obtain their bacilli by the following graphically expressed routes, the significance of which will be further elaborated.

1. *Fingers or utensils to mouth.*
   This is the route of direct contact.
2. *Fingers, to food, to mouth.*
3. *Fomites, fingers, food, to mouth.*
4. *Flies, food, to mouth.*
5. *Fomites, flies, food, to mouth.*

These four latter routes are those which constitute the means of indirect contact cases.

In the group of direct contact cases fall particularly those individuals who have to do with the care of the sick. Nurses and

physicians have long been recognized to be very much more liable to contract typhoid fever than ordinary individuals. The reason for this greater susceptibility is evident. Their fingers come in contact with the bodies of typhoid patients and with their excreta, and in instances where rigorous cleanliness is not followed, these contaminated fingers readily transmit infection to the mouth. Physicians and nurses, moreover, are not only themselves open to infection through this channel, but other non-typhoidal patients whom they may handle in practice or in the hospital may be infected in the same manner. This latter possibility accounts in part for the spread of typhoid fever, which may occur from bed to bed in hospital wards. Fingers, however, are not the only means of direct contact infection of this type. Any object that has come in intimate contact with the patient may serve as a direct method of transmitting infection, particularly those instruments that have been placed in the mouth, such as thermometers, cups, spoons and glasses, which, if utilized by another individual without careful cleaning, may transmit the disease. The eating of food remnants that have been left by typhoid cases, particularly as it occurs among children in the home, may serve as a means of transmission. Kissing is another possibility that has been mentioned as a similar channel.

The direct contact cases are said to be peculiarly severe, which may be attributed to the unaltered virulence in the microorganism, which suffers no deterioration outside of the body. Cases contracted in this manner are due peculiarly to lack of cleanliness of a grade that should be avoidable. Direct infection may also occur from carriers, although this is not so likely a route in typhoid fever as it is in other infectious diseases which also have carriers, as diphtheria, cerebrospinal meningitis and poliomyelitis. In these latter infections the diffusion of the infective agent is more indiscriminate and its nature is less well recognized.

The first mode of indirect contact transmission, as represented by the formula—fingers, food, mouth—is characteristic of those cases which emanate from carriers. In the first place, as has been mentioned, women predominate as typhoid carriers, and they are, of course, the individuals particularly concerned in the preparation of food, and it is through food stuffs prepared by such individuals that the disease may be transmitted in some instances to large numbers. Food, moreover, is not only a relatively direct route to the mouth of the individual, offering little harmful influence in the external life of the typhoid bacillus, but may actually serve as a culture medium for the microorganism. A strik-

ing instance of this mode of transfer which brings out the latter possibility has been reported by Sawyer [1] in an epidemic of typhoid which occurred in Hanford, California, where a carrier prepared a dish of spaghetti which was allowed to stand over night and then browned on the following day and served to a large number of people at a church dinner, of whom ninety-three came down with the disease. Subsequent laboratory experiments showed that spaghetti prepared in this manner allowed an enormous multiplication of the microorganisms, which were not subsequently killed by the heat necessary to brown the dish. The handling of milk by carriers is another mode of transmission of this sort, which frequently gives rise to epidemics of considerable size, following the routes of distribution of milk. Localized water supplies may also be infected, as was the case in an epidemic on shipboard likewise reported by Sawyer,[2] in which it was found that a carrier had infected the water butt, from which other members of the crew drank, by dipping his hand into the water to fill his cup.

Personal infection occurs in this indirect contact manner as well as the infection of other individuals in those cases where people who have handled typhoid fever patients or their excreta may contaminate their own food through a failure to wash the hands. We may here also for convenience include the majority of cases of laboratory infection from cultures of typhoid bacilli and also from the organs of those dead of the disease. The route in these cases may, of course, be simply direct, as in the first type of contact infection that has been studied, or may be indirect through soiled fingers to the food of the individual who becomes infected.

The third rubric that we have given includes another link in the sequential chain which serves to transmit typhoid bacilli from feces to the mouth. It differs from the last group in introducing fomites, which have become infected with feces or other excreta from typhoid cases. The cases of typhoid which occur among washerwomen are an example of this type of infection. When these women are called upon to wash the unsterilized linen from typhoid cases, they may readily infect their hands and subsequently their food and come down with the disease. Hospital cases of typhoid are also at times traceable to such a source through contaminated linen or towels that have been used on typhoid patients. Armies are particularly prone to indirect contact infection of this type. The danger of abandoned camps has been repeatedly emphasized by military observers (Vincent and Muratet). A

recent report of Uhlenhuth, Olbrich, and Messerschmidt would attribute the typhoid fever that occurred in German troops in France in the great world war to the contact infection from contaminated localities. Army blankets have likewise been shown to transmit typhoid several months after being used on a case of the disease, and clothing used by soldiers, either dead or recovered from typhoid fever, may also serve as a mode of transmission. Firth and Horrocks (Whipple, p. 68) have shown that typhoid bacilli will survive on khaki or serge cloth for two or three months. Perhaps the greatest danger, not only in camps, but also in civil cases, particularly in the country, is the danger of contaminating the shoes by walking on ground over which typhoid excreta have been scattered, and subsequently transmitting the bacilli by the fingers from the shoes to the mouth. The importance of this type of contact infection in armies may be gathered from the estimate that 62.8 per cent of all the 20,000 cases which occurred in the Spanish-American War were due to infection of this sort, and observations in the Boer War indicate that the percentage was probably as high there also.

In the fourth and fifth types of contact transmission an animate agent of a new sort is introduced. Sedgewick [2] was perhaps the first (1892) to suggest that flies are of importance in the spread of typhoid fever. The report on the epidemics of typhoid in the Spanish-American War by Reed, Vaughan and Shakespeare made it very evident that the swarms of flies which had free access to the uncovered latrines, and subsequently to the food eaten by the soldiers afforded a very significant means by which at least some of the cases were transmitted, although the majority of them could be attributed, as has been stated, to a type of contact infection that has been just discussed. These observations, whereas significant, are at best only circumstantial, and it remained for the work of Hamilton to prove conclusively that the ordinary house fly, musca domestica, in houses in which cases of typhoid fever exist could be shown to contain typhoid bacilli. These observations have subsequently been confirmed by Ficker and by Klein. The failure of certain authors to confirm these observations should not be taken as militating against them, since this is one of the instances where a positive finding in competent hands is of far greater significance than many negative results. Epidemiological studies in many places have only confirmed the importance of flies in the spread of typhoid. Epidemics of army typhoid in South Africa and in India (Chapin) have been shown to have a direct relation to the number of flies that were present, and Odlum

(Vincent and Muratet) found that the systematic killing and guarding against flies caused a rapid cessation of an epidemic in India in the midst of a typhoid season, which again returned when such precautions were omitted. Hill has stated that typhoid fever occurring in the lumber camps of Minnesota likewise seems to bear a direct relation to the number of flies that are present and allowed to have access to unprotected water closets (Chapin).

Flies may transmit the typhoid bacillus either by the mechanical sticking of the organisms to the exterior of the insect or by the passage of the bacillus through the gastro-intestinal tract and its elimination in the feces. It has been claimed (Whipple) that under artificial conditions flies may retain the typhoid bacillus in their bodies for twenty-three days. The possibility of other insects serving as transmitters of typhoid is rendered possible by the almost incredible experiments of Dutton, who allowed bed bugs to bite a typhoid fever case and subsequently produced the disease in healthy individuals by the bite of these same insects.

Water Infections in Typhoid

Routes 6, 7, 8

6. Water to Mouth.—We have already seen that contaminated water was the first recognized and apparently the most significant vehicle of typhoid infection. Reduction in typhoid morbidity during recent years has been largely at the expense of the water-borne cases, owing to improvement in water supplies, and yet water still remains the most important single channel by which the typhoid bacillus reaches the human body. Estimates vary as to the total percentage of typhoid cases that are referable to water infection; somewhere from ten to forty per cent in the opinion of different authors. The importance of water in producing epidemics of typhoid is even more marked than in the production of individual cases. According to Spitta, Schüder found that of 640 typhoid epidemics seventy-two per cent were due to water, and Schegendahl found that of 682 cases about thirty-three per cent were water-borne. Not only is water an important channel in conveying typhoid fever, but, conversely, typhoid is the most important water-borne disease.

Typhoid bacilli in excreta may reach a water supply in several ways. Feces may be thrown directly into the water; excreta may be deposited on the surface of the ground and washed therefrom into a water supply, particularly into wells by rains; or the overflow from privies in heavy rains may likewise be washed into drinking

water. Perhaps the most common method of water contamination from sewage is by means of surface water or by subterranean percolation of the sewage, which may extend for very considerable distances, particularly if the soil is chalky in nature. An accidental connection between sewer pipes and water pipes may occur, or regurgitation of sewage may take place in faulty valves of a water supply. The dumping of mud near the intakes in supplies of lake water has at times given rise to epidemics.

The typhoid bacillus survives in water for varying periods of time, which increase directly with the purity of the water. In sterile water the organism may survive for as long as three and one-half months, although it is not to be supposed that any marked multiplication of the organisms takes place, as water cannot be regarded as a culture medium for the microorganism. As the pollution of the water increases, the survival of the typhoid bacillus is shortened. In river water it has been estimated by Park and Williams to last for from two to seven days. It survives longer in water that is still than in water that is in motion, which is the reason why running streams have a certain though very limited tendency to purify themselves. Warm water is more favorable for the resistance of the typhoid bacillus than is very cold water. Although the majority of typhoid bacilli disappear from water in a very short period of time, the resistant minority, which may be sufficient to produce infection, may survive for several weeks or months. Exposure of shallow water to the rays of direct sunlight is, of course, an inhibiting factor on the resistance of bacteria.

The proof that cases of typhoid fever are due to water infection is of two general sorts. In the first place, typhoid bacilli have been found in the water which gives rise to epidemics. This isolation of the typhoid bacillus from naturally contaminated waters is, however, extremely difficult, and has actually been accomplished only seven or eight times. Even in those cases where the organism is found, it is not always possible to prove that it was present at the time the cases under investigation were infected. The suspicion of any given source of water usually rests upon presumptive tests through demonstration of sewage pollution by the presence of colon-like bacilli in such materials. By far the more usual and satisfactory method of proving the water origin of typhoid lies in the epidemiological evidence which in certain instances at least is extremely convincing. In the most convincing cases it may be definitely proven that typhoid excreta have reached the water supply, a demonstration which is directly connected in point of time and distribution of the water with the

outbreak of a group of cases. Less convincing evidence is present in those cases in which a water supply, known to be contaminated or probably contaminated, determines in its distribution a series of typhoid cases which disappear when the water supply is changed. The cases of typhoid occurring after water contamination may be grouped under two general headings. A single accidental contamination, as, for instance, when excreta are thrown into the water, may be followed by an explosive and acute epidemic of typhoid, which subsides rapidly; or in the second case a continuous endemo-epidemic form of typhoid may exist in which sporadic cases are interrupted by acute exacerbation in the form of larger or smaller epidemics. It has also been shown by Winslow that water-borne epidemics of typhoid are frequently followed by a number of contact cases, to which form of spread he has given the name of "prosedemic."

The general characteristics of cases attributable to water contamination, then, are that they are frequently in epidemic form, and that such epidemics begin in an explosive manner and are localized to the areas supplied by the water under consideration. Water-borne typhoid epidemics occur characteristically in cities, although they may readily occur through well contaminations and in more localized form in country towns. Another characteristic which frequently draws attention to the water supply as the cause of an epidemic of typhoid is its occurrence out of the regular typhoid season. Any considerable increase in cases in winter months, for example, would at least lead one to suspect a source of this kind.

Contaminated water produces typhoid, at least as we are considering it at this point, by entrance directly into the gastro-intestinal tract. It is, of course, primarily through drinking that such cases occur, although brushing the teeth in contaminated water may produce the disease. Dilution of contaminated water in the ordinary manner by wine, a device sometimes adopted with the idea of sterilizing the water, has been shown experimentally to be ineffective in killing the typhoid bacillus. It has been shown that soda water and other soft drinks will retain living typhoid bacilli for considerable periods of time, although such beverages are probably rarely or never contaminated under natural conditions, and are of little significance in the actual spread of the disease.

A few outbreaks of typhoid fever have been traced to ice contaminated by the typhoid bacillus. Cases due to this cause must be extremely rare, as the freezing of water tends to purify it, and those instances that are definitely known to be due to this source

have been shown to be due to gross contamination on the surface of natural ice ponds or to careless handling by unclean hands. Park and Williams have shown that the great majority of typhoid bacilli of various strains, when artificially frozen, are destroyed in one or two weeks; there remain, however, a resistant minority of something like one-tenth of one per cent of the organisms which survive as long as five weeks. The best evidence that ice is an infrequent cause of typhoid fever is that there is no marked increase in the morbidity rate in large cities during the early months of summer when ice is freely used.

7. Water, Food, Mouth.—Infections following this course are simply by one degree more complex than those that have been considered under the last heading. Contaminated water may transmit the typhoid bacillus either through admixture or through its use for cleaning receptacles to various types of food, which in turn become sources of infection. Among the most notorious infections of this type are those which occur from shell fish. Oysters in particular have been for many years suspected of being a possible source of typhoid infection. It remained, however, for Conn in 1894 to demonstrate that an epidemic of typhoid which occurred among the students in Wesleyan University could be directly traced to oysters consumed at a banquet, which had been fattened over a period of several days near the outlet of a sewer. It has been a common custom to fatten or bloat oysters by shifting them after removal from their original beds to a place where they are exposed to a fresh water stream. Such streams when near large centers of population are, of course, grossly contaminated with sewage. The epidemic described by Conn has been several times paralleled not only in this country but in France (Chantemesse, 1896) and England. Certain places on the English littoral, in particular Belfast, Brighton and other towns, have for many years had endemic or residual typhoid cases, which form a very considerable per cent of the total number, and which may be in all probability traced to the eating of raw shell fish, oysters, mussels and cockles. Experiments on the resistance of typhoid bacilli when artificially placed in oysters show that they will survive for from five to nine days.

Another indirect source of contagion from contaminated water is in the consumption of raw vegetables such as water cress, celery and radishes, which either have been washed with water or have been subjected to a forced growth by fertilization with night soil or contaminated water.

One of the great sources of typhoid in its epidemic form is con-

taminated milk. Milk comes to serve as a vehicle for the typhoid bacillus in three general ways. It may first of all be handled by carriers and so infected from their hands, and this infection may take place either on the farm, which is the more usual, or subsequently during the transportation of the milk to market. This contamination of milk through carriers is perhaps the more usual and important means, and we have already mentioned its existence in another place, but milk may also be contaminated either through washing the cans in contaminated water or by actual adulteration with such water, usually from an infected well. The spreading of epidemics of typhoid through milk was mentioned as early as 1858 by Taylor, and further insisted on by Ballard in 1870. Milk epidemics are characterized by occurring over the route supplied by some given milkman, and by the occurrence of several cases in a given house supplied with milk from this source. The disease itself occurs particularly in children and in women, who constitute the principal milk drinkers. The onset of the disease is characterized by a short incubation period, and its course is usually mild, which has been attributed to the attenuation of the pathogenic properties of the microorganism through its growth in milk. Inasmuch as milk drinking is more or less of a luxury, milk epidemics occur more particularly in the families of the well-to-do. There is no question that epidemics and cases of typhoid through milk are considerable in number. Trask (Rosenau) in 1908 found a description of 317 milk epidemics, or something like 1900 cases in the United States alone. Schüder in Germany found that 110 epidemics of the 640 which he has described were due to milk. Rosenau, who was concerned in the careful study of epidemics which occurred in Washington and which were investigated by the Public Health Service, thinks that something like ten per cent of all the cases for at least several years in that city were due to milk. Such a percentage of the total number of cases has been frequently accepted and quoted, but the figures are criticized by Chapin, not only on the basis of experience in other places, but on the basis of the figures in the Washington report itself; he is inclined to attribute a much smaller although still considerable rôle to milk in the spread of typhoid fever. Chapin, further, is inclined to question the generally accepted notion that milk epidemics are in part due to the fact that milk serves as a culture medium for the multiplication of the organisms originally contaminating it. There is no question, of course, but that sterilized milk is an admirable culture medium, but there are experiments which go to show that raw milk has during several hours at least a distinct inhibiting

effect on the growth of the typhoid bacillus. As Chapin points out, if multiplication of the bacillus took place readily in milk, we should expect to find many more cases in the large cities due to this source, which, however, is not characteristic of such forms of the disease. Milk epidemics of typhoid spread rather over a short milk route in smaller towns, and there are practically none in the larger cities where milk is brought from a considerable distance and where much more time is allowed either for the multiplication of the organisms or, on the other hand, for their disappearance.

Typhoid bacilli in milk are in all probability not readily killed when such milk is added in the ordinary proportions to tea or coffee, and such drinks may therefore serve as a further vehicle of infection in cases of this sort.

8. Soil, Water or Food, Mouth.—We have incidentally considered for the most part the features of an indirect transmission of the typhoid bacillus in this way in our consideration of the more direct route from water to the human body (*Heading No. 6*). This route is probably more usual, as we have already intimated, than from feces or sewage directly to water. The former route represents more particularly the acute outbreaks of the disease, as we have stated. There are, however, certain prolonged epidemics which may be attributed to the further resistance of the typhoid bacillus in soil and its gradual and continual percolation into water sources. Chapin, who has thoroughly reviewed the experimental evidence as to the survival of Bacillus typhosus in the soil, concludes that these experiments show that although there is no multiplication in the soil, the organism may persist there for something like seventy-four days. Curschmann would lengthen this period to five and one-half months, and other authors would agree with him (Vincent and Muratet).

Air and dust have both been mentioned as sources of infection in typhoid fever, more particularly in the early consideration of the transmission of the disease, as in the work of Budd and Murchison. It is probable, however, that most of the cases attributed to infection of this sort were in reality contact infections, which in their lack of knowledge concerning the active agent in typhoid fever, these authors were unable to appreciate. The typhoid bacillus may survive drying and be alive in dust for considerable periods of time. There is not, however, any conclusive evidence that would show that transmission by dust through the air produces any considerable number of the cases of typhoid fever.

Relative Importance of Various Routes of Infection

As to some extent summarizing certain authoritative opinions on the relative percentages of cases of typhoid fever which may be traced to definite sources, we may at this point present certain of them in tabular form.

TABLE VI

THE PERCENTAGE OF SOURCES OF TYPHOID FEVER

	Contact	*Water*	*Milk*
Rosenau	6–17	35	10
Chapin	10–40	10–15	0.2%
Whipple	30	40	25
Kober	—	80	—
Spitta	—	33	—
Frosch	65	23.7	

It will be noted in this table that whereas there is marked difference in opinion as to the number of cases which may be due to contact, there is more or less agreement as to the considerable number of cases, something like one-third, which are traceable to water. It is understood that these percentages represent, so far as these authors are able to estimate, the conditions of the present day. In former times the cases attributable to water are, as we have mentioned, far more numerous.

GENERAL FACTORS WHICH INFLUENCE THE OCCURRENCE OF TYPHOID FEVER

There are a number of factors which determine the success or failure of typhoid infection in its extension from one individual to another. These factors may be divided into two general categories, extrinsic and intrinsic, in accordance with whether they are resident without or within the individual whose susceptibility to infection is determined by their resultant interaction.

Extrinsic Factors.—Any condition operative on the life of the typhoid bacillus after it has left the human body tends markedly to affect its success in reaching and producing infection in a second individual. In general, the most important of these conditions are dependent on the directness of the route followed by the typhoid bacillus from one individual to another, which route in turn includes the various factors which are antagonistic or favorable to the growth of the bacillus. These conditions have been fully dis-

cussed in the previous sections of this chapter. It may in general be stated that any unfavorable influence which tends to reduce the numbers or the virulence of the typhoid bacillus would markedly influence its possibility of producing typhoid fever.

One of the most significant and earliest observed characteristics of typhoid fever is its seasonal occurrence. It has long been recognized that the disease occurs most frequently in late summer and autumn, although exception to this statement should be made in the case of epidemics due to gross pollution of water or food supplies, the causation of which is, indeed, indicated by their extra-seasonal occurrence. The reasons which underlie the characteristic seasonal occurrence of typhoid are by no means certain. Warm weather, particularly when combined with humidity, would, of course, provide a more favorable environment for the growth of the typhoid bacillus outside the body, but it seems certain that no such simple variation suffices to explain the predominance of cases during this season. It appears that not only the incidence but also the severity of typhoid cases is increased during warm weather. Three additional factors may be suggested as correlative with this increase in temperature: first, the larger number of flies which are present during this season; second, the increased consumption of liquids during warm weather; and, third, the vacation habit which leads to unaccustomed surroundings with ignorance of possible sources of infection.

Geographical locality would seem to play little or no rôle in the occurrence of typhoid fever. The disease is ubiquitous, and epidemics have been described not only in the tropics but in equal number in temperate zones. And, again, the disease occurs indiscriminately in the plains and in the mountains, the ordinary variations in temperature, apart from seasonal variations, apparently having little effect on the occurrence of the disease. The ubiquity of typhoid fever is further evident in the fact that apparently all races of men are equally susceptible. It is true that certain authors have given evidence which would tend to show that some races, notably East Indians, Japanese and Arabs, may under certain conditions show an apparent insusceptibility to typhoid. The low morbidity rate of typhoid in a country like Japan, however, may be more directly attributed either to dietary differences, or possibly to acquired immunity owing to more frequent incidence of the disease in childhood, rather than to a racial insusceptibility. In those other instances where it is apparently shown, as in the case of the Arabs, that the endogenous race is much less susceptible than an alien race in the same country, the factor of non-

acclimatization, which we shall presently consider, would seem of more importance than a relative racial insusceptibility.

Intrinsic Factors.—It seems certain that under like external conditions with equal infecting doses no two individuals are equally susceptible to typhoid infection. This is evidenced by the fact, first, that in any given epidemic the severity of the disease will vary markedly from one individual to another, and, secondly, by the fact that under conditions of greatest exposure, whereas the majority of individuals fall victims to the disease, a small number remain uninfected. These variations in susceptibility are primarily individual, but may also in certain instances, as we have already mentioned, appear to be racial in character. The French authors in particular, for example Vincent and Muratet, and Brouardel and Thoinot, are inclined to attribute a real physiological difference in the defense of various races against the typhoid bacillus, but these differences, which undoubtedly are evident under certain conditions, would seem more easily attributed to variations in degree of exposure to infection or to acclimatization, as we have already stated. The most important factor affecting individual resistance to infection is the existence of immunity acquired either through recovery from the disease or through vaccination, the significance of which we shall discuss in a later place. The French authors we have mentioned further believe that a resistance of this sort may be acquired through a process of mithridatisation, brought about by the swallowing of repeated small doses which are insufficient to produce the disease but which give rise to a resistance to it. Apparently this conception exists in a less concrete form among many physicians who are inclined to attribute their failure to contract typhoid fever, in spite of great exposure, to constant association with typhoid fever cases. It would seem that evidence for an acquired immunity of this sort is no more than suggestive.

The most important individual factor in determining susceptibility to infection with the typhoid bacillus is the question of age, as has been recognized by all competent observers. Infants are relatively insusceptible to typhoid, although the disease may occur in the fœtus in utero and in a few instances in very young children. These instances are perhaps more frequent than is realized, owing to the mildness of the attack and to consequent failure in diagnosis. The incidence of the disease in all events increases very slightly from one to five years of age, but somewhat more markedly after this period to the age of puberty. The majority of cases of typhoid fever may be grouped about the twenty-

first year. According to Curschmann, four-fifths of all the cases occur between the fifteenth and thirty-fifth year. This author further finds that fifty-three per cent of his cases occurred between the ages of fifteen and twenty-five, a figure with which Murchison essentially agrees, and from which statement there is no marked variation in the experience of other authorities. The incidence of the disease decreases markedly from the fortieth year onward, although the severity and morbidity rate increase.

There is apparently some difference in opinion as to whether there is a varying susceptibility to typhoid infection in regard to sex. The majority of authors apparently have found no great difference in the number of males and females that have come under their observation. Others, for example Brouardel and Thoinot, and Curschmann, regard adult males as more susceptible than females of the same age. The latter viewpoint would seem more reasonable in view of the greater exposure to unguarded sources of infection to which the more active life of the male exposes him. Typhoid fever attacks particularly well nourished, active persons, apparently not only through their greater chances of exposure but also through some physiological difference which renders them more susceptible to the invasion of the bacillus. On the other hand, exhaustive diseases and other infections would seem to render individuals relatively less susceptible to infection. In a somewhat similar manner it has been generally agreed that pregnancy and lactation in women tend to render them less likely to be affected by the disease. Certain of the French authors would attempt to establish a family susceptibility to typhoid, owing to the undoubted fact that a number of cases may and frequently do occur in the same house. There seems no reason, however, to regard such occurrences as due to any cause other than greater exposure.

Another interesting and apparently generally accepted cause of increased susceptibility is lack of acclimatization. It has been repeatedly noted that recent arrivals in large cities are more susceptible to typhoid fever than the inhabitants. Louis found that seventy-nine per cent of his cases in Paris occurred in individuals who had lived for twenty months and less in the city, and Chomel in a somewhat similar manner found that sixty-seven per cent of his cases occurred in those resident for less than two years. A similar lack of acclimatization is evident in the city cases of vacation typhoid, as they are called, which account for a considerable percentage of the cases in large cities which are rigorously careful in respect to their water supply. Here, of course, it is difficult to

demonstrate conclusively that the city dwellers have acquired typhoid in the country because they were not acclimated, and a more reasonable explanation in most instances would be that they had suffered greater exposure in drinking of contaminated water supplies and the like. We find it somewhat difficult to accept the explanation which Vincent and Muratet, and Brouardel and Thoinot have offered for the cases due to non-acclimatization. These authors regard the preponderance of cases among recent arrivals in any given community as due to the fact that these individuals, although they may be insusceptible to the strains of the typhoid bacillus in their home localities, are unaccustomed to the particular strains where they contract the disease. The most reasonable explanation for this group of cases must, we think, again be greater exposure and ignorance of proper water and food supplies.

Work and fatigue, and possibly also psychic disturbances, such as anxiety and grief, may to some extent render the individual more susceptible to infection.

Certain professions are distinctly more liable to typhoid fever than others. First among them are, of course, soldiers, and with them as with the other more susceptible professions, exposure again must be regarded as the most important factor. Soldiers, furthermore, in addition to the extreme danger from unguarded water supplies are particularly affected, owing to the fact that they are at precisely the age during which the majority of cases occur. They further suffer from the lack of acclimatization to which reference has been made, and are frequently exposed to fatigue and overwork. Washerwomen, particularly those engaged in the care of hospital linen, and nurses and physicians, who are in constant contact with typhoid cases are also very prone to take the disease.

CHAPTER V

THE PATHOGENESIS OF TYPHOID FEVER

We are now in a position to consider more minutely that disease which the typhoid bacillus produces in the human body. As has been repeatedly intimated, we are not concerned in this treatise with a consideration of typhoid fever as a clinical entity awaiting diagnosis, but rather as a conflict between antagonistic elements represented by the typhoid bacillus and the human body. It is by this attitude that we conceive that the ultimate aims of diagnosis and therapy are most successfully to be realized. For this purpose we shall follow the course of the typhoid bacillus in the human body so far as we may, rather than attempt detailed consideration of the symptoms of typhoid fever, except in so far as they may be employed in explaining the actual mechanism of the disease.

GENERAL SYMPTOMATOLOGY OF TYPHOID FEVER

As introductory, however, to a more detailed consideration of those phases of typhoid infection concerning which we may collect sequential data, we present at this point a brief and general outline of the symptomatology of the disease as a whole. The clinical picture of typhoid fever may be sketched chronologically as marked off into four more or less definite periods. During the first or incubation period, the nature of which will be more fully discussed presently, there are no definite, or at least no diagnostic or very indicative symptoms present. The distinctive symptoms of the disease are usually dated from the occurrence of actual fever, but there usually precede certain more or less well defined subjective disturbances which are briefly as follows: headache, listlessness, pain in the legs and back and anorexia, which may be extreme and be accompanied by nausea and even by vomiting. The initial symptoms are not infrequently ushered in by a chill. In general, it may be said that these premonitory symptoms are gradual rather than abrupt in their onset.

The second period covers the first febrile period of the disease, and lasts, roughly, from a week to ten days. This period, known as the stadium incrementi (Jochmann), or the period of ascending

oscillations (Vincent and Muratet), is characterized by a gradually rising temperature, which is higher each afternoon by a degree or so, and has morning remissions which may frequently fall to normal. During this period the temperature usually rises to a maximum of 103° or 104° F. This increasing fever is accompanied by a slow pulse of 100 to 110 which is of low tension and characteristically dicrotic. As subjective symptoms may be noted vertigo, buzzing in the ears, headache, which may be severe, and a gradually increasing apathy and feeling of weakness. Epistaxis is not infrequent but by no means regular. The abdomen becomes distended, the tongue is white and furred and the bowels may either be constipated or diarrhea may be present. Not infrequently slight râles over the chest give evidence of a mild bronchitis. The leucocytes frequently are slightly increased in number to a count of perhaps 10,000 to 11,000 to the cubic millimeter. This period is accompanied by the beginnings of those pathological changes which are characteristic of the disease. The patches of Peyer show hyperemia followed by hyperplasia; the solitary follicles also begin to project beyond the surface of the intestine; the mesenteric lymph nodes are swollen and reddish; the liver is enlarged and hyperemic; and the spleen also begins to enlarge during this first febrile period.

The third period of the disease represents the febrile plateau during which the temperature is at its maximum, 103° to 105° or even more, and is not characterized by any considerable remission during the course of the day. This is the stadium acme, so-called, or fastigium. It lasts, roughly, through the second and third weeks. During this period the headache usually becomes less, but the mental processes are cloudy, giving rise to the characteristic typhoidal condition (τῦφος, a cloud). The apathy increases and delirium may become more or less marked, particularly at night. Diarrhea is usual and the excreta become more fetid. Tympanites may become marked. The tongue is brownish and dry. Ulcerations may occur in the pharynx and mouth. The enlarged spleen becomes clinically palpable. Rose spots occur in the majority of cases, either singly or in small successive crops. The blood picture is characterized by a leucopenia with a relative increase of the mononuclear cells and absence of eosinophiles. The loss of weight becomes considerable. The pulse is more rapid and less dicrotic in quality.

The lesions of the disease during this period go on in their characteristic evolution. The swollen Peyer's patches become necrotic and sloughing, with small ulcers which usually coalesce and extend

lengthwise of the gut, frequently penetrating to the submucosa or the muscularis. The mesenteric lymph nodes are still more swollen but grayish in color and show patches of necrosis. The liver becomes less hyperemic and rather flabby, and shows on section small grayish nodules which are found to be due to collections of proliferated endothelial cells. Parenchymatous degeneration is also present in both liver and kidney. The spleen increases to its maximum size, which is from one and one-half to three times the normal. Hemorrhage and perforation are among the complications which may occur during this period.

The latter period of the disease, extending usually from the third week onward, is characterized by a falling temperature, and is known as the stadium decrementi or the period of descending oscillations. The afternoon maximum decreases by fractions of a degree daily, and the morning temperature falls more rapidly until it reaches normal or even subnormal. The mouth and tongue become clean. Polyuria takes the place of suppression of urine, which may have occurred previously, and the appetite gradually returns. Necrosis of the intestinal lesions may increase and lead to hemorrhage and perforation, failing which, in favorable and usual cases healing begins to take place.

The actual complications, hemorrhage, perforation, and particularly relapse, may occur after several days of normal temperature, and the other sequels, thrombosis, osteomyelitis, cholecystitis and the like, which we will discuss in more detail, also take place during or following this convalescent period.

THE INCUBATION PERIOD

In common with all other infectious diseases, there occurs a definite incubation period following the ingestion of typhoid bacilli, before the development of the symptoms of the disease. This incubation period, in the case of diseases whose causative agents enter the body through the gastro-intestinal tract, and subsequently invade the entire body, should, properly speaking, be regarded as beginning when the microorganism leaves the gastro-intestinal tract through some portal of entry to initiate the process which characterizes its presence in the body. The mere presence of the microorganism in the gastro-intestinal tract should theoretically not be regarded as the beginning of the disease itself, any more than the presence of the tetanus bacillus on the skin of the body would be so considered. Owing to the difficulty, or, indeed, the impossibility in most instances of determining the

exact moment at which the typhoid bacillus enters the body proper from the intestine, it has been customary to regard the incubation period as beginning with the ingestion of the micro-organisms. And even in this case the estimation of this latent period is more difficult in the case of typhoid fever than in almost any other disease, excepting in those instances where known contaminated food or drink has been ingested.

The simple presence of typhoid bacilli in the intestine does not in itself constitute infection with the typhoid bacillus, as is evident from a consideration of those healthy and recovered carriers who show no symptoms of the disease. In other words, the organism may live as a saprophyte in the intestine for indefinite periods without initiating any disease process.

The usual period of time between ingestion of material containing the typhoid bacillus and the occurrence of the first symptoms of the disease has usually been regarded as between ten days and two weeks. Curschmann states the incubation period to be one to two or three weeks, Murchison two weeks or more, and McCrae three to twenty-three days. The possibility of a short incubation period has been recognized very distinctly since the time of Budd,[2] who speaks of a series of cases in which the incubation period seemed definitely to have been about four days. Murchison also speaks of cases with a short incubation period, although his information seems to be less definite regarding them than was Budd's. The acceptation of the classical two weeks interval would seem to be founded on somewhat indefinite evidence and on a basis of cases in which the transmission has been through contact or water pollution. In both these instances we have reason to believe that the actual number of bacteria ingested is relatively small, and more recent experience shows not only that the incubation period may be as short as Budd has stated, but that the actual duration probably bears an indirect relation to the number of bacteria that have entered the gastro-intestinal tract.

In the case of laboratory infections it is easier not only to estimate the number of bacteria that have been swallowed, but to know with great accuracy the time at which the organisms were actually taken into the body. Kisskalt's [1] study of cases of typhoid laboratory infections apparently does not bear out the idea that the incubation period is shortened by a large dose of bacteria. In a careful summary of fifty cases of this sort in which the mode of infection was in the most instances known, the usual duration of the incubation period was about fourteen days, al-

though there are cases of five, six and eight days recorded. In these cases it must be taken into consideration that although the original dose consciously taken into the mouth was usually large, vigorous efforts were made in most instances to destroy the ingested bacteria, which must at least have been to some extent successful.

In a case which occurred in our own laboratory an assistant, while injecting a goat with a thick suspension of mixed living cultures of recently isolated typhoid bacilli, received through the spurting of a temporarily blocked syringe a considerable amount of the injection mass on the left cheek and conjunctiva. Two days later she felt distinct malaise, and on the fifth day was ill in bed with a temperature of 104°, at which time the typhoid bacillus was isolated from the circulating blood. In the epidemic reported by Sawyer in Hanford, California, of ninety-three people, who had partaken of a dish of Spanish spaghetti which had been prepared by a typhoid carrier the day previous to eating, and in which the bacteria had multiplied by a process of incubation, as was subsequently shown by laboratory experiments, over half of the cases showed symptoms before the eighth day, the first one on the third day, twelve on the fifth and nineteen on the sixth. Epidemics caused by contaminated milk, when compared with those produced by contaminated water, are characterized by suddenness and violence of onset (Whipple). It is well known that whereas typhoid bacilli tend to decrease in polluted water, they increase rapidly in milk, which serves as an admirable culture medium.

This probable relation between the size of the infecting dose and the shortness of the incubation period renders Vaughan's [2] admirable hypothesis of fever still more acceptable. Vaughan has assumed that the incubation period preceding the onset of fever in the infectious diseases is due to the lapse of time required for the formation of specific proteolytic ferments, the subsequent action of which on the bacteria liberates poisons which cause the fever. Under usual conditions of infection with small dosage it would take the classical ten days interval for the production of effective ferments, just as it does for the maximum formation of antibodies under conditions of artificial immunization. We know, however, that this antibody formation may be markedly accelerated. Strong hemolysins, for instance, can be formed in four or five days when proper doses of blood are given animals intravenously (Gay and Fitzgerald). Smith has claimed that the antibodies responsible for the Abderhalden reaction may actually

be produced in a few hours. The modern work on protein therapy which is assuming significance, as we shall later see, in typhoid and other acute infections, would seem unquestionably dependent on the rapidity with which ferments of this type can be mobilized. The condition of antityphoid immunity is perhaps best explained in a similar manner.

THE PORTAL OF ENTRY

The typhoid bacillus may be found at almost any point in the gastro-intestinal tract during the course of the disease. Drigalski [1] obtained pure cultures from the tonsils and tongue, and also from the stomach, in spite of the acid reaction there present. Indeed, it has been shown that small amounts of hydrochloric acid have very little effect on the growth of the typhoid bacillus (Kitasato). There is, however, no reason to believe that the typhoid bacillus actually increases in numbers anywhere in the intestinal canal (Forster [1]). The evidence, indeed, is quite to the contrary. During the latter stages of the disease, when the organisms are present in large numbers in the feces, it may still be shown that the numbers in the lower part of the canal are much smaller than in the upper portions. Cultures taken at successive levels by Drigalski and by Forster and Kayser [1] have shown that whereas the typhoid bacillus is present in practically pure cultures in the duodenum, it decreases in numbers and purity as one descends toward the lower end of the small intestine and into the colon. This diminution is brought about not only by a failure of the organism to multiply, but by the antagonism of the colon bacilli normally present in the canal. It has recently been found by Nissle [1] that strains of colon bacilli differ markedly in their antagonistic effect in symbiosis with typhoid bacilli, those strains which produce the greater amounts of lactic acid giving the higher "antagonistic index," and he has actually suggested the importation of such active strains of the colon bacillus in combatting, or, indeed, in preventing typhoid fever. It may be that the failure to produce a septicemia with Bacillus typhosus in the smaller laboratory animals in feeding experiments is due to a still more active antagonism of this sort (Bezzola and Vallardi). The overgrowth of colon bacilli may be favored by a carbohydrate diet, which is one of the reasons for the success that has attended the recent methods of high calory treatment in typhoid.

The small number of typhoid bacilli which constitute the original infecting dose are in all probability either soon destroyed or absorbed through the portals of entry. At all events, they do

not usually occur in the excreta in sufficient numbers to be found on ordinary examination. We know that the percentage of cases in which the examination of the feces becomes positive increases with the duration of the disease, being greatest during the necrotic period of the intestinal ulcers, roughly, from the eleventh to the twentieth day of the fever. Their occurrence in large numbers during the stage of necrosis has no direct relation to the necrosis itself, for the organisms do not multiply to any extent in the necrotic areas, nor are they primarily eliminated through them. There is no question that the numerous organisms in these latter stages of the disease have been excreted with the bile into the intestine. They reach the gall bladder, as we shall see, from the circulation. It may happen that the typhoid bacilli in the bile are not present in large enough numbers to survive until they reach the cecum and so be detected in the stools, until very late in the disease. Instances have been reported by Conradi [2] in which they were not found until eleven to eighteen weeks after the first symptoms. On the other hand, it is known that they may exceptionally occur during the incubation period of typhoid fever (Conradi,[2] Mayer.[1]). These individuals who excrete the typhoid bacilli before they show evidence of the disease constitute the so-called precocious carriers, which from the standpoint of hygiene are the most dangerous ones in producing contact infections, owing to the fact that they are not recognized to be dangerous. Conradi [1] found that fifty-eight per cent of the contact infections from typhoid cases occurred in the first week. The early occurrence of the typhoid bacillus in the stools of such individuals does not, however, in any way reverse our statement as to the failure of the organisms to multiply in the intestine. It simply means that the organisms have entered the body proper from the intestinal canal, have actually multiplied there, in all probability have been present in the circulating blood, and have in all events been eliminated through the gall bladder precisely in the fashion that regularly takes place later in the course of the fever.

The mere presence of the typhoid bacillus in the gastro-intestinal tract of man is not sufficient to cause typhoid fever. We have evidence of this fact from our knowledge concerning the existence of healthy carriers, individuals who have never suffered, so far as known, from typhoid fever, who in the majority of cases show no evidence in their blood serum reactions that they have undergone such an infection, and yet harbor the typhoid bacillus in their intestines. The absence of a history of typhoid fever, how-

ever, does not preclude the possibility that the typhoid bacillus has actually passed through the body of such an individual, without causing the characteristic symptoms of the disease. Simple gastro-intestinal upsets with or without a fever are undoubtedly in some instances true cases of typhoid infection, and it is known that the typhoid bacillus may reach the gall bladder presumably through the circulation, without calling forth or before evoking any definite symptoms of typhoid fever. Perfectly healthy individuals have indeed been detected with typhoid or paratyphoid bacilli in the circulating blood (Conradi,[2] Busse, Mayer, and Ebeling).

It has frequently been assumed that the lower part of the small intestine, particularly those structures which respond characteristically to typhoid infection, namely, Peyer's patches, represent the portals of entry in the disease, but whatever proof of this exists is essentially indirect. The infecting microorganism must proceed somewhere from the gastro-intestinal tract to the internal organs, there to set up the lesions and to evoke the symptoms which are characteristic of this malady, but it is by no means certain that the usual lesions of Peyer's patches have anything to do with the entrance of the microorganism. These lesions are in all probability eliminative in character, and probably are evident only after the microorganism has gained a hold in the general circulation, and with certainty only after the actual entrance of the microorganism into the body from the gastro-intestinal tract. It has been shown experimentally by Ribadeau, Dumas and Harvier that typhoid bacilli are excreted into the intestine after intravenous injection through the intestinal wall, and particularly in places that are rich in lymphoid tissue like the appendix. It is interesting in this connection to note that appendicitis, particularly of a mild degree, is of relatively frequent occurrence in typhoid (Hare and Beardsley). According to Wolfsohn,[1] appendicitis due to Bacillus typhosus may be the only evidence of typhoid in individuals rendered resistant through vaccination.

It has been suggested by some observers that the tonsils or lymphoid structures in the pharynx may represent the true portals of entry. Drigalski [1] reports an epidemic which he studied in which forty per cent of the cases began with an angina, and he was able to obtain pure cultures from the throat in most of his cases. Tonsillitis and sore throat are not infrequent beginning complications of typhoid, and have been noted repeatedly since the classical works of Louis and Jenner.[3] A number of other writers have mentioned the tonsils as possible portals of entry (Brion and

Kayser). Curschmann * is inclined to regard tonsillitis as an unusual accompaniment of typhoid, although he found it with great frequency in certain epidemics. Further attention has been drawn to the upper part of the gastro-intestinal tract as a possible portal of entry by the occurrence of ulcers in the pharynx, as noted by Louis,† Jenner,[3] ‡ and Klebs.[3]

Whatever may be the exact point of entrance of the micro-organism, it seems fairly certain that the lymphoid apparatus, whether of the pharynx or of the intestine, is the first structure affected, and remains the characteristic point of localization of the typhoid infection (Kolle and Hetsch; Sanarelli, Jochmann, and Kutscher). The mesenteric lymph nodes apparently are swollen before any visible change has taken place in the intestinal mucosa, and, granting that the portal of entry lies through this mucosa, it seems certain that the entrance may take place without any visible lesion (Meyer). Cases of typhoid without intestinal lesion have been reported in considerable numbers (Posselt [1]), and will later be considered in other connections. Such cases are not infrequently characterized by swollen mesenteric nodes, even when there are no lesions in the intestines (Chiari and Kraus). Of course, the failure to find any macroscopically visible lesion of the intestinal mucosa does not rule out minute abrasions which might be sufficient to allow the entrance of the typhoid bacillus. An ancient idea of the causative relation between intestinal worms and susceptibility to typhoid has been recently brought forward again by Barabaschi. In this author's experience oxyuris or trichocephalus were present in the intestines of ninety-six per cent of his typhoid cases, whereas in healthy people they occurred in only twenty-one per cent, and he suggests that they injure the mucosa sufficiently to allow easier penetration of the bacillus. Considering the widespread susceptibility of unprotected individuals to typhoid infection, as evidenced in epidemics, the assumption of some necessary injury to the mucosa to permit infection seems superfluous. Apart from the fact that the mesenteric nodes may be swollen without any evident portal of entry, it has also been shown that these nodes are the first to be swollen in the course of the disease (Baumler), thus indicating clearly that they are the first affected. Levy and Gaethgens found, moreover, that while cultures from the mesenteric glands in typhoid autopsies were invariably positive, and while they were nearly always macroscopically changed, they frequently failed to find the micro-organisms in other lymph nodes. Banti succeeded in isolating

* Loc. cit., p. 202. † Loc. cit., p. 135. ‡ Loc. cit., p. 63.

the typhoid bacillus from the spleen and lymph nodes in a case which showed no other lesions. Southard and Richards have described a case of typhoid meningitis with recovery of the organism from the brain and mesenteric lymph nodes only. The latter were swollen and were the only organs suggesting typhoid fever at autopsy.

LOCALIZATION OF THE TYPHOID BACILLUS IN THE BODY DURING THE COURSE OF THE DISEASE

The lymphoid apparatus of the small intestine is, then, the beginning and the most characteristic localizing point of typhoid infection. The changes in the mesenteric lymph nodes, as evidenced by visible enlargement, must be of very early occurrence in the disease. Delafield and Prudden report an autopsy in the forty-seventh hour of the disease where the only lesion found was such a nodular swelling. The changes in the finer structure of the lymph nodes in typhoid fever is at once interesting and of considerable significance in throwing light on the mechanism of the process itself. We are indebted primarily to Mallory [1] for having pointed out the exact nature of the changes in the lymphatic system in typhoid fever. He has described with great minuteness the structure of those nodular swellings or "lymphomata," as they had been previously called, which he finds due not to proliferation of lymphoid but of the endothelial cells in the lymph nodules. These cells show signs of active mitosis wherever they occur in the spleen, lymph nodes, liver or bone marrow. Mallory's supposition that the cause of this proliferation is the liberation and action of endocellular toxin from the typhoid bacillus is perhaps correct, although he brings forward no experimental evidence in its support. The limitations of the histological method are evident in those observations, which lead him to state that the typhoid bacillus is not characteristically present in these specific lesions. The exact contrary may be shown to be true, as we have already stated, when systematic cultures are taken from these nodes and compared with cultures from any other part of the body. It becomes evident that the lymph nodes remain, in conjunction probably with the bone marrow and gall bladder, and perhaps the spleen, the reservoirs and foci of proliferation of the typhoid bacillus throughout the course of the disease.

It is of great importance to identify more certainly these reservoirs of the typhoid bacillus, as throwing light upon the mechanism of the disease. The typhoid bacillus is found, as we know,

in the circulating blood at almost any period in the course of the disease, but more particularly in its early stages. The organisms multiply probably in the lymph nodes and overflow into the circulation, whence they are swept to various other parts of the body, there to be destroyed, or by a metastatic process to give rise to additional foci of re-infection. The typhoid bacillus has been found in the thoracic duct, presumably en route from the lymph nodes to the general circulation (Dehu). We shall later consider in more detail the percentages of positive blood cultures at different stages in the fever in connection with the chapter which deals with diagnosis. Suffice it to state here that the bacillus on entering the body from the intestine reaches the general circulation with great rapidity, probably during the incubation period, as has already been mentioned, and is practically always to be found there in the earliest stages of the fever. It is probable that in healthy carriers who give no history of typhoid fever the typhoid bacillus may have passed through the general circulation and into the gall bladder, where we know that it continues to proliferate and thereby to account for the permanent or temporary dissemination of the germs. This probability is rendered more likely by our knowledge of the occurrence of primary gall bladder infections with or without subsequent typhoid fever (Posselt [1]).

The almost constant finding of the typhoid bacillus in the blood, and, particularly, its presence even in those cases without characteristic intestinal lesions, has led to increasing agreement in regarding this infection as a septicemia or bacteremia. The two terms have been used indiscriminately. It is called a septicemia by Posselt, Besancon and Philibert,[1] and by Sanarelli, and a bacteremia by Drigalski, by Kolle and Hetsch, by Jochmann and others. The latter term is undoubtedly the correct one, if we accept the opinion of Roger that bacteremia should be employed to include both septicemia and pyemia; in other words, any condition in which the microorganism occurs both in the blood stream and in localized or metastatic foci. Such is precisely the condition which occurs in typhoid fever where the microorganism, although not multiplying in the circulating blood, is found there very frequently. It not only fails to multiply in the blood but is destroyed there, and in all probability with great rapidity, since it is known that even normal human blood has the property of destroying the microorganism, a property which is increased during the course of the disease in proportion to the success with which the individual reacts to the invading pathogenic agent. This increase in bacteriolytic power accounts for the failure to obtain cultures with

so great frequency in the latter stages of the disease, excepting in those cases of grave or fatal prognosis. Jochmann has laid great emphasis on the number of resistant typhoid bacilli as obtained in plates from the circulating blood, as indicating the actual condition and prognosis of the individual case, and there is some evidence from the observations of Flexner to believe that the typhoid bacillus rapidly increases in the terminal stages of fatal cases, when the bacteriolytic activity of the blood diminishes. This is further indicated by the work of Schottmüller,[1] who found that in the fatal cases there is a progressive rise in the number of colonies to death.

General experience further agrees with Schottmüller that the typhoid bacillus is not found in the circulating blood after the end of the afebrile period of typhoid fever. The difficulty lies in explaining the persistence of the fever after the blood culture has become sterile, which is the regular occurrence in every recovering case. The fall in the number of bacteria in the circulating blood as the disease progresses is accompanied in a general way by a rise in the antibodies likewise present, at least in so far as they may be determined from the content of the serum in agglutinins. This would seem to suggest that typhoid bacilli continue to enter the circulation from the reserve foci in lymph nodes, spleen and bone marrow, but are so rapidly destroyed as to render blood cultures sterile, although, and indeed through this rapid destruction, the fever persists. Schottmüller has also shown that in some cases recrudescences in the fever may be accompanied by reappearance of the organism in the blood.

The Cause of the Fever in Typhoid.—The destruction of the microorganism in the circulating blood in large numbers is very probably the cause of the fever which is so characteristic an accompaniment of the disease process. According to Vaughan,[1] it is the successive splitting of foreign proteins which would account for fever in general, and he has been able to produce a similar continuous fever in rabbits by the injection of a relatively harmless foreign protein, egg white, an observation which was extended by Friedberger and Mita, who obtained similar results with bacterial proteins. In agreement with this hypothesis are the observations of Bergey which show that the pyrogenic action of the typhoid bacillus is due to intracellular rather than to soluble toxins. It should not be overlooked in this connection that afebrile forms of typhoid of undoubted authenticity have been described by numerous authors and succinctly presented by Hare and Beardsley. These cases frequently present all the other characteristic signs of

the disease, positive blood cultures and Widal, enlarged spleen, roseola, and the like, and may be quite as severe as the ordinary febrile cases. So far as we are aware, no explanation of this anomalous form of the disease is forthcoming.

Metastatic Foci of Typhoid Bacilli.—Typhoid bacilli that have entered the circulating blood from the original foci in lymph nodes are then spread in a metastatic manner to various parts of the body, with predilection for certain tissues. Among these tissues are lymph nodes, bone marrow, gall bladder, spleen, periosteum, and kidneys. They are present also in the rose spots, where they occur not in the blood vessels but in the connective tissue spaces (Kolle and Hetsch). These multiple foci where the bacteria succeed in multiplying serve as reservoirs for continuous re-infection or re-invasion of the circulation, with continuance of the fever, for recrudescences of the disease in the form of relapse, and for the production of complications and sequels, and are of still greater general significance in the spread of the disease through carriers. It is interesting to note that when these tissues are properly stained, the bacteria in the metastatic foci appear characteristically in clumps which are often of considerable size.

We may consider in some detail the individual significance of these various metastatic foci. The continued presence of nests of the typhoid bacilli in the lymph nodes, the spleen and bone marrow, is characterized, as we have already mentioned, in the majority of cases of typhoid fever by the appearance of certain definite and well recognized, specific lesions in the nature of endothelial proliferation. These reactions may be simple reactions of injury, but more likely represent a purposeful multiplication of those cells (macrophages) which we may suspect have to do with the elaboration of antibodies. Reactions of this type and the occurrence of those characteristic lesions in Peyer's patches which are dependent upon this endothelial proliferation are no indication of the severity of the infection itself (Jochmann). Indeed, it is probable that proliferation of the endothelial cells is a beneficial process and indicative of successful resistance. The ulceration of Peyer's patches is largely a mechanical affair brought about, as Mallory has shown, by the shutting off of the blood supply in these areas through occlusion of the vessels by these endothelial masses, and to some extent aided by the action of the endotoxins of the typhoid bacillus. Fatal terminations in typhoid fever through hemorrhage or perforation must be regarded as accidents of the disease rather than indications of the severity of the infection, such as is truly represented by those deaths

designated as due to toxemia. It would be interesting in this connection to know more definitely the severity of those unusual cases of typhoid fever which are characterized by a septicemia without intestinal or other specific lesions. That they may be severe is, of course, evident from the fact that the only ones we have recognized have had a fatal termination, and whether such atypical cases occur with greater frequency in recovered individuals cannot, of course, be determined. At all events, these three organs, bone marrow, spleen and lymph nodes, are the organs where, next to the gall bladder, typhoid bacilli are found with greatest regularity at autopsy, even in those cases where the circulating blood is sterile (Kutscher). Similar results have been obtained by Lüdke [1] in inoculated guinea pigs, who found that the bacteria are present in the spleen and bone marrow where they increase after they have left the circulating blood, which he regards as similar to the condition during the latter stage of human typhoid fever. In unreported experiments from this laboratory it has been found that the chronic typhoid carrier state in rabbits following intravenous injection is characterized by persistence of typhoid bacilli in large numbers, not only in the gall bladder but also in the bone marrow. Whereas the bacilli are found for the first few days in spleen, lymph nodes, blood, bile, and bone marrow indifferently, they soon disappear from the blood, lymph nodes and spleen as the agglutinins rise in the serum. On the other hand, they increase in the bile and bone marrow, where enormous numbers are evident in plates. This condition would seem to offer still further analogy between this rabbit condition and human typhoid (Gay and Claypole [1]). Quincke and Fraenkel have both obtained positive cultures from the bone marrow with regularity in cases of typhoid.

The Bone Marrow in Typhoid

The organisms may continue to multiply in the spleen and bone marrow, and perhaps also in the lymph nodes, even after the temperature has returned to normal. There would seem to be definite relation between the persistence of splenic tumor and the occurrence of a relapse (Sterzing). The bone marrow is of particular interest in relation to sequels of the disease, particularly those of a surgical nature, which in this localization take the form in decreasing frequency of periostitis, necrosis and caries (Keen).

There would seem to be a direct relation or sequence in the elective affinity of the typhoid bacillus for the bone marrow, the changes produced in the cells there, and the characteristic leucocyte pic-

ture in the well developed disease. Longcope has made a detailed study of the bone marrow changes in typhoid and found them to consist of hyperplasia of the lymphoid cells and endothelial phagocytes as in the lymph nodes, and in the presence of disseminated necroses. In the cases that were complicated by perforation and peritonitis diffuse degenerative changes of the blood-forming cells with marked edema and congestion were added to this picture.

In direct sequence would follow the characteristic blood picture of leucopenia, relative increase of large mononuclear cells and aneosinophilia which, as pointed out by Naegeli and by Thayer, occurs in ninety-five per cent of all cases and is of diagnostic value. The leucocytes, which may show a slight increase early in the disease, by the second week fall to four to five thousand, and may in extreme cases reach two thousand or below. We have seen one case with complicating laryngitis and later pneumonia in which the count was one thousand only, some days before a fatal termination.

A sudden rise in the leucocytes may be indicative of a complication, although it has been shown by Kast and Gutig and by Longcope that this is by no means the rule. Even perforation with general peritonitis, according to these authors, usually fails to cause a rise of leucocytes above seven thousand. A gradual return of the leucocyte count to normal, in particular when associated with the re-appearance of eosinophiles, is indicative of recovery. The sharp leucocytic crisis artificially induced by the intravenous injection of typhoid vaccine is, as we shall later see, frequently accompanied by temporary or permanent symptomatic benefit in practically any stage of the disease.

The Gall Bladder in Typhoid Fever

The most interesting metastatic focus in the body, both in relation to the course of the disease itself and particularly in relation to its sequels, is the gall bladder. The liver and the bile have certain very definite antagonistic action against certain invading microorganisms (Posselt [2]). It would appear that the inhibiting effect of the liver on bacterial growth is due to its action as a blood filter and also to its content in bile. Bile seems to have definite bactericidal effect upon certain microorganisms such as the streptococcus, pneumococcus and the tubercle bacillus (Zehden). On the other hand, organisms of the colon-typhoid group, and particularly the typhoid bacillus seem to have a peculiar affinity for the gall bladder and for bile. Reference has already been

made to the rapidity with which the typhoid bacillus may be found in the gall bladder in cases of human typhoid infection. The very first symptoms, and indeed the only symptoms, of typhoid infection may be referable to the gall bladder by the occurrence of jaundice (Posselt [1]), by cholecystitis, by the occurrence of a liver abscess, or by localized peritonitis due to perforation. In the majority of cases, however, the typhoid bacillus reaches and remains in the gall bladder without evoking either immediate or delayed symptoms. At all events, the bacilli are present in the gall bladder in practically every case of typhoid fever (Chiari[2, 3]; Kolle and Hetsch; Forster and Kayser; and Kutscher). It is now generally agreed that the organisms reach the gall bladder through the circulating blood in a descending fashion, originally pointed out by Chiari [4] on the basis of human cases, and later through the study of a similar condition in rabbits. In studying the latter condition it was found by Chirolanza that rabbits given an injection of typhoid bacilli in the vein would show the microorganism in the gall bladder in at least two hours, and even when the cystic duct was tied. We have obtained similar results within half an hour.

The typhoid bacillus reaches the gall bladder promptly through the circulation, and, as we have stated, even in cases which show no symptoms of typhoid fever. This, we believe, accounts for the production of healthy carriers. The condition of precocious carrier, which may occur in the incubation period of typhoid fever, is likewise undoubtedly due to the fact that the typhoid bacillus has already entered the general circulation and been eliminated in increased numbers through the gall bladder even before symptoms of the disease occur. We know, furthermore, very definitely that the increasing numbers of typhoid bacilli during the course of typhoid fever are due to the increasing multiplication and elimination through the bile into the intestine, as is clearly evidenced by the repeated observations, to which we have referred, that show that there are more organisms present in the upper sections of the intestine than in the lower. There is evidence that although bile in its original condition may not inhibit the growth of the typhoid bacillus, it becomes an even more favorable medium for its growth through the deposition of certain albuminous substances caused by the growth of the organism in the walls of the gall bladder. Perhaps the greatest significance of the occurrence and growth of the typhoid bacillus in the gall bladder lies in relation to its persistence there after recovery from the disease, with its etiological importance in the

formation of gall stones, and in the production of the temporary or permanent carrier condition.

THE TOXINS OF THE TYPHOID BACILLUS IN THEIR RELATION TO THE DISEASE PROCESS

We have spoken of the toxins of the typhoid bacillus in the third chapter and have incidentally attributed certain of the results of human infection, such as fever and the like, to these toxins, but have for the most part been concerned in the localization and multiplication of the microorganism itself in the body. Any toxin production must, of course, presuppose and be dependent on the growth of the bacillus itself, or, perhaps better, on its destruction and disintegration, which thereby liberates its endotoxins. Certain symptoms and results in typhoid fever have been attributed directly to toxins, and we may question indeed if all symptoms are not really referable to these somewhat indefinitely understood substances. Headache, fever, circulatory disturbances, the nervous and mental manifestations of the typhoidal state seem definitely toxic symptoms, and certain deaths in the disease are likewise attributable to toxemia. We have already referred in part to the probable mechanism of the characteristic lesions. The intestinal necrosis and ulceration are probably due, as we have stated, to the occlusion of the blood vessels by proliferated masses of endothelial cells, and perhaps both directly and indirectly through this hyperplasia, are due to toxins. The parenchymatous changes which may occur in heart muscles, liver and kidney are likewise attributable to the toxins (Delafield and Prudden). It is interesting to note that the nature of the intestinal lesions was probably correctly interpreted as eliminative by Sanarelli on the basis of animal experiments. This conception seems now almost certainly correct in view of our present understanding of typhoid fever as a bacteremia and in consideration of further experimental evidence with endotoxins, as given by Arima and others.

A further word might be said in relation to the nature of the typhoid toxins themselves. We have already seen that although the typhoid bacillus may produce a type of soluble toxin, its harmful effects must in large part be attributable to the so-called endotoxins. The exact nature of these endotoxins is now in dispute, as to whether they are specific products of the individual race of bacilli or are simply the non-specific poisonous molecular group which Vaughan has shown to be present in all proteins, as may be shown by their chemical cleavage. Vaughan's further

description of the mechanism by which the poison is liberated in the body by ferments, especially engendered during the incubation period, seems almost certainly the correct explanation not only of the mechanism of fever but of all effects in the disease due to toxin liberation. It is further supplemented by the work of Friedberger and his collaborators along the same lines in explaining the nature of anaphylatoxin formation. A more extensive discussion of this subject would lead us too far afield, and we will refer interested readers to the chapters in Zinsser's "Infection and Resistance," which deal with these problems in an authoritative manner,* and content ourselves with his admirable summary: † "The present status of the question, it seems to us, may be summed up as follows: It may probably be accepted as a fact that anaphylatoxin production occurs and accounts for toxemia, altogether or in part, in all diseases in which bacteria invade the tissues or circulation; in addition to this, soluble toxins produced by the bacteria still living and uninjured may add a further specific element to the condition—in some diseases; whether or not specific preformed endotoxins participate in the production of bacterial toxemia cannot be definitely stated. It is not, however, a necessary assumption."

THE COMPLICATIONS IN TYPHOID

At this point it may be well to consider in a general way certain of the complications of typhoid fever, although reference has been made incidentally to certain of them in attempting to describe the mechanism of the course of the disease itself. Certain of these complications might properly be classed under the sequels which will be treated in a following chapter, although an effort has been made at a somewhat arbitrary separation of the two on the basis that complications occur during the course of the disease or immediately following it, whereas sequels occur at a somewhat more remote period subsequent to recovery from the malady. As we have already mentioned, typhoid fever is characterized by a high percentage of complications, perhaps in from twenty-five to thirty per cent of all cases (Cummings and Brown; Noblecourt and Peyre). Their significance is most striking when we consider them as causes of death, and we find very definite statements as to the relative importance of complications and of the typhoid process itself in this respect. Curschmann has estimated that the typhoid infection per se, or the severity of intoxication, as he

* Loc. cit., Chapters II and XVII. † Loc. cit., p. 422.

calls it, which is equivalent to the word toxemia as used by other writers, is the greatest single cause of death, producing from thirty to fifty per cent of the fatal cases. This estimate, based on his own cases, is probably excessive, or at least does not thoroughly represent more modern conditions where we recognize that typhoid is a somewhat less virulent disease. Whipple states that the complications of typhoid are responsible for two-thirds of the fatal cases. Dopfer and Holscher agree singularly well in attributing fatalities to complications in 75.5 per cent and seventy-six per cent, respectively. At any rate, it seems safe to state that the majority of deaths in this disease are due to its complications.

The deaths from the severity of the typhoid infection itself are in a general way due to one of three causes, either to the hyperpyrexia or to the effect of the toxins of the typhoid bacillus on the central nervous system, or, again, to its action on the circulatory system, affecting, as it does, the heart muscle and the blood vessels. In all instances the result is attributable to toxins from the typhoid bacillus, the potency of which in turn is, partly at least, referable to the actual number of organisms, and partly to the virulence of the infecting strain itself. It must be admitted that reference to the toxins of the typhoid bacillus, as will appear from previous chapters, is not strictly speaking a very exact one, since we have very little precise information as to the nature of these poisonous substances. In general it may be said, however, that severe and fatal cases of typhoid are accompanied, at least in their later stages, by a high bacterial count in the circulating blood. At this point may be mentioned the sudden deaths in typhoid, usually without definitely known causation. Vincent and Muratet estimate them to occur in one to three per cent of cases.

Important complications of typhoid fever may be listed categorically and more or less in the order of frequency of their occurrence as follows: relapse, hemorrhage, perforation, pneumonia, nephritis, laryngitis and necrosis of the larynx, pleurisy, cholecystitis possibly accompanied by perforation, parotitis, meningitis, appendicitis, thrombosis, abscess and pyemia, gangrene and splenic abscess. Certain of these complications are worthy of a more detailed consideration as throwing light on the actual mechanism of the disease.

Hemorrhage and Perforation

Hemorrhage and perforation may be considered together inasmuch as they are more or less due to the same set of operative

causes. These characteristic and important complications of typhoid bear no definite relation to the severity of the disease itself, but are obviously accidental and due entirely to mechanical causes. They may occur in the mildest cases, and, indeed, are very likely to occur in those cases which are so mild as to be ambulatory, thereby giving ample opportunity for greater strain. We have already mentioned the explanation which Mallory would give as underlying necrosis and ulceration of Peyer's patches, which in turn is the underlying cause of both hemorrhage and perforation. Mallory's explanation of the extensive necrosis which may occur is that it is brought about by mechanical obstruction of the blood vessels through proliferation of the endothelial cells, which, as he has definitely shown, characteristically proliferate in the course of the disease. Another mechanical factor of great importance in hemorrhage and which apparently has not been sufficiently recognized, is the actual blood supply of Peyer's patches themselves. Professor Herbert M. Evans, who has made a particular investigation by special injection methods of the pattern of the blood supply of the human intestine, has been kind enough to furnish me with a statement of his as yet unreported studies as follows.

"The particularly disastrous nature of the hemorrhage due to erosion of the Peyer's patches (agminated follicles) may find its simplest explanation in the peculiar anatomical arrangement of the local blood supply. Indeed, the arrangement of the blood vessels in the neighborhood of an agminated follicle is so altogether peculiar that an injection of the arterioles alone in such an area, and any subsequent treatment which renders transparent the bowel wall, would enable us to predicate positively the exact position of the patch of Peyer. This is due to the fact that the tiny special arterioles of the Peyer's patch leave their various places of origin from the main submucosal plexus when still some little distance from the margins of the patch and pursue an almost unbranched course to the patch. There are great numbers of these tiny straight coursing arterioles which thus radiate from all sides into the patch running almost parallel courses and so frequent that a considerable number exist in the length of a centimeter or two. Thus erosion near the margins of the patch would easily open up a far greater number of arterial sources for hemorrhage than in any other like area of the bowel."

Numerous figures are available in the clinical literature as to the frequency of occurrence of these two important complications of typhoid, but it is important here to give simply an average of such

figures which do not vary to an extraordinary degree among themselves. As regards perforation, it may be assumed on the basis of numerous figures that it occurs in three or four per cent of all cases. As a cause of death, however, the percentage referable to this unfortunate complication is distinctly higher. Murchison estimates that 11.38 per cent of all the deaths in typhoid fever are due to perforation, whereas McCrae would attribute twenty per cent of the deaths to this cause. Curschmann's figures lie between the two, being from fourteen to nineteen per cent.

Hemorrhage occurs, according to Homolle, who studied the reports from ten thousand cases in this respect, in 4.65 per cent of all cases. The general average from other writers would lie between five and ten per cent, although in certain groups as high as thirty per cent of the cases have shown hemorrhage (Whittington). Hemorrhage, therefore, is distinctly a more frequent occurrence than perforation, as might be expected, owing to the more superficial level of ulceration required to bring it about. But, on the other hand, hemorrhage is likely to be a less serious manifestation than perforation, for it is the cause of death, according to Curschmann, in only six to nine per cent of the cases of typhoid. It is interesting to note in this connection the observations of Hare and Beardsley, which have led them to state that hemorrhage when not fatal will not only not be an unfortunate symptom, but even a beneficial one. The mechanism of the benefit produced by hemorrhage is by no means certain, but the suggestion may possibly be made that it might be due to the hyperleucocytosis which frequently accompanies this complication, and which, as we shall see more in detail when we consider the specific treatment of the disease, is of distinct beneficial effect.

Relapses

The most interesting complications of typhoid infection are the relapses. The true relapse of typhoid fever must be distinguished from the spurious relapse or recrudescence which mean simply a temporary rise in the fever during the descending temperature period. The true relapse occurs after an interval of several days' normal temperature, that is to say, after the disease, as indicated by the fever, has terminated. This interval may be prolonged from a few days to four or five weeks of apparent normal convalescence and recovery. The relapse itself is practically a repetition of the original disease, although in ordinary course it is usually shorter and less serious. The mortality in relapses is low, according to McCrae something like 2.9 per cent, and according to Cursch-

mann a little under five per cent. Relapses usually run a shorter course than the original disease, frequently of only a few days. Many or all of the original symptoms and diagnostic signs of the preliminary attack of typhoid fever occur in the relapses. The rose spots may reappear (Bartlett), a new crop of intestinal lesions may occur (Adami and McCrae), and as a rule the typhoid bacillus is present in the blood, although cultures just preceding this period may have been sterile for a number of days. A number of relapses may occur; as many as four or five have been recorded. The percentage of cases in which relapses have been found varies considerably; Murchison had three per cent in his cases, whereas Stertzing had over thirteen per cent in a more recent group. According to Vincent and Muratet, they are particularly prevalent in the so-called abortive form of typhoid, the fever of short duration, about which more will be said later in connection with typhoid in the vaccinated and in connection with specific treatment.

Relapses are undoubtedly due to the overflowing of typhoid bacilli from their localized metastatic or ultimate foci in the body, which have already been discussed in detail. The particular localization in respect to relapse has been attributed by different writers to different places in the body; thus v. Fütterer and Chiari would attribute them to a persistence of the microorganisms in the gall bladder, a suggestion which must, at least in part, be true, and which was more crudely expressed in pre-bacteriological days by Moore, who thought them due to re-absorption of infectious material from the bowel, which will perhaps mean nothing more than a re-entrance of typhoid bacilli that have been discharged from the gall bladder through the intestinal wall. Stertzing regards the persistence of an enlarged spleen as prognostically indicative of an oncoming relapse, which would indicate that the foci of bacteria in this particular organ give rise to the subsequent overflowing into the circulation. Another characteristic sign that has been noted by this author is the persistence of the leucopenia, which would seem, however, to indicate the bone marrow as the source of reinfection, a locality rendered still more likely in view of the observations that we have already cited in respect to this tissue.

A word may be said in reference to the occurrence of pneumonia as a complication of typhoid fever. It apparently occurs in from ten to fifteen per cent of all cases and may either be of the lobular or the lobar type. There are several predisposing factors in typhoid which would lead to the ready occurrence of pneumonia, such as the initial bronchitis which, as already mentioned, is a common symptom, the feebleness of respiration and circulation and the

recumbent position which leads to a settling of blood in the dependent parts of the lung. The pneumonia when it does occur may be due either to the typhoid bacillus or to an intercurrent infection from one of the various types of pneumococci. This complication may occur early or late in the disease.

EXPERIMENTAL TYPHOID FEVER IN ANIMALS

The complete experimental verification of the typhoid bacillus as the true etiological agent in typhoid fever was delayed for many years after its isolation, owing to repeated failures to produce the analogous syndrome in laboratory animals, as would be required in complete fulfilment of Koch's celebrated postulates. We know now that this particular postulate may be expected to fail of verification in many of the exclusively human diseases, or at least can be verified only in anthropoid apes.

A survey of the attempts to produce typhoid fever in the lower animals, both in pre-bacteriological days and subsequent to the discovery of the typhoid bacillus, need not detain us long. Non-specific congestions of the intestine were induced in animals by Magendie (1823) and others following the intravenous injection of putrid substances. Similar results, based on the conception of typhoid fever as a non-specific spontaneous putrefactive disease were obtained by D'Arcet and others. Murchison [1] fed a pig for six weeks on the dejecta from typhoid cases, and at autopsy found the animal fat and with normal intestines.

We have already referred in the first chapter to the early experimental work of Klebs, who claims to have produced a hemorrhagic infiltration without ulceration in the cecum of rabbits by means of cultures of the typhoid bacillus grown on gelatine. Gaffky, as we know, was unable with his more certainly pure cultures of the bacillus to obtain such results when the organism was given either by the mouth or by intravenous injection. Fraenkel and Simmonds,[2, 3] by giving large amounts of pure cultures of the typhoid bacillus to mice, produced rapidly fatal symptoms with swelling and ulceration of the follicles of the small and large intestine, together with less definite lesions of the liver, kidney and spleen. They very properly, however, did not regard their results as similar to typhoid fever in man. It was later shown by the work of Sirotinin and by Brieger, Kitasato and Wassermann that results of this sort are due to the toxins of the bacillus, and similar results can be produced by preparations of these toxins from which the bacteria have been removed. In none of these

experiments that have been quoted do the observers claim to have produced in animals a disease with a course resembling that seen in human typhoid. Sanarelli injected sterilized cultures of Bacillus coli intraperitoneally at the same time that the typhoid bacillus was introduced subcutaneously. This led to a typhoid culture of exalted virulence, which in small amounts produced infiltration of Peyer's patches which were found to contain typhoid bacilli, as did the mesenteric glands and the spleen. Remlinger found that by prolonged feeding of rats and rabbits on vegetables soaked in water containing typhoid bacilli he was able to induce a continued fever, lasting from ten to twelve days, accompanied by diarrhea, loss of appetite and wasting. Four of eight rabbits experimented on became sick. One was killed on the twelfth day and one died on the twelfth day of fever. Three or four gave positive agglutination reactions, and autopsies on two rabbits showed swelling of spleen, lymph glands and Peyer's patches. Similar results were obtained by Atlassoff, who obtained intestinal lesions in young rabbits resembling those of human typhoid by feeding them with pure cultures of the microorganism, or, more particularly, with such cultures mixed with certain strains of torula.

Reference should here again be made also to the work of observers like Arima, who produced swelling and hemorrhage of the agminated follicles in rabbits by the injection of endotoxins from the typhoid bacillus, which observations we personally have been able to confirm. We may also refer to the rabbit carrier condition which we have already discussed, and which we shall use as illustrative of the human carrier condition in a succeeding chapter. This condition, as we have previously pointed out (Gay and Claypole [1]), resembles in many respects human typhoid fever, omitting the stage of infection through the intestine and the intestinal lesions which usually accompany the human disease. When certain strains of typhoid bacilli are injected into the circulation of rabbits, the animal continues to excrete them through the gall bladder for long periods of time. The organisms are found at first in practically any organ of the body and in the circulating blood, but soon disappear from the blood and most of the tissues, with the exception of the bone marrow and the gall bladder. The agglutinins rapidly rise in the circulating blood as the number of microorganisms diminishes. These carrier rabbits usually undergo progressive emaciation until death, which takes place in two or three months. Fever does not in our experience accompany the rabbit syndrome. Such experiments, taken in conjunction with the ones we have already mentioned, would seem to show that

many of the characteristics of human typhoid infection can be reproduced in rabbits, although it would be incorrect in all probability, in spite of the results of Remlinger and Atlassoff, to claim that true typhoid fever can be produced in these animals.

Attempts made to produce typhoid fever in monkeys or the higher apes, were not successful until recently. Sutton as early as 1883 had called attention to a disease in three monkeys which he regarded as identical with human typhoid fever. The description of the disease and autopsy findings in two lemurs that died a week apart in the same cage after suffering from profuse diarrhea seems very circumstantial. In one animal death was due to perforation and at autopsy extensive ulcerations of the follicles were found adjacent to the ileocecal valve. Hemorrhage led to the death of the second animal, which showed similar lesions extending through the cecum. In 1904 Grünbaum attempted to infect chimpanzees by feeding them with pure cultures of the typhoid bacillus and with stools from typhoid patients. His results, however, were at best only suggestive. In 1911 Metschnikoff and Besredka,[1] after vain attempts along the line of Grünbaum's experiments, succeeded in producing a syndrome in the higher apes that must be accepted as essentially similar to the typhoid fever of man. Their experiments were undertaken primarily for the purpose of testing the efficacy of certain methods of antityphoid vaccination and also with the possibility in mind that typhoid fever might conceivably be produced not by the typhoid bacillus but by some filtrable virus adhering to it, as had been proved to be the case in a somewhat similar disease, hog-cholera. Metschnikoff and Besredka failed at first to infect chimpanzees with pure cultures of the typhoid bacillus, but on feeding them with stools from typhoid cases they were able finally to produce in these animals a characteristic fever accompanied by diarrhea and positive blood cultures and Widal. The filtrates of stools as well as killed cultures of the typhoid bacillus failed to produce this disease. They then employed cultures isolated from chimpanzees that had been infected in this manner, and found that such cultures would then succeed perfectly in reproducing the disease in other chimpanzees. They succeeded, indeed, in fifteen out of sixteen instances, and their single failure is in itself interesting as offering definite analogies to normal human carriers. They succeeded, then, in the majority of cases in producing a characteristic fever and three deaths due to the infection itself. In all instances the Widal reaction was positive in these animals as well as the blood culture. Diarrhea was a regular symptom and at autopsy the mesenteric

lymph nodes were enlarged and Peyer's patches hypertrophied, although they were not ulcerated. The spleen was in no case notably increased in size. They subsequently succeeded in producing a somewhat similar disease in two Macacus monkeys out of over fifty that were tried.

These experiments, then, of Besredka and Metschnikoff fulfil completely the last of Koch's postulates, which prescribes that a microorganism to be regarded as the causative agent in any given disease must be able, when inoculated in pure culture in laboratory animals, to initiate the same disease from which it was obtained.

CHAPTER VI

THE DIAGNOSIS OF TYPHOID FEVER

An early diagnosis in each suspected case of typhoid fever is important, not only for the welfare of the patient but for the good of the community at large. If the case proves to be typhoid, it is imperative for the good of the patient that he should be kept in bed and properly nursed, and that his diet and treatment should be intelligently regulated. The extension of the disease to others may, when its nature is recognized, be absolutely prevented. The accuracy of purely bed-side diagnosis in typhoid is, in the hands of the experienced, considerable. Such accuracy, however, is more particularly true of cases in retrospect; an early clinical diagnosis can never be made with certainty. The diagnosis of typhoid on a clinical basis depends, as in other diseases, on a process of symptom-matching; whereas no single symptom of the disease is in itself pathognomonic, the group of symptoms is in general characteristic.

The characteristic clinical symptoms of typhoid fever have been briefly outlined in the previous chapter. Their detailed discussion and their comparison with the symptom complex of other diseases affords the material of which clinical treatises are made. Such discussion is neither germane to, nor primarily helpful in this attempt to develop a mechanistic conception of typhoid fever. No modern physician should wish, or be obliged to make a diagnosis of typhoid fever without laboratory aid, and it is doubtful if he would ever be justified in arriving at a positive diagnosis when a complete series of laboratory examinations fails to confirm his clinical opinion. Clinical suspicion of typhoid is, however, the necessary incentive to laboratory diagnostic tests and the suggestive symptoms which lead to such suspicion should, therefore, be sketched.

Any fever lasting over a period of days, accompanied by malaise, headache, insomnia, and diarrhea, ushered in by chill or nose-bleed, particularly when unaccompanied by definitely localizing symptoms, except possibly pain on epigastric pressure or sore throat, may be suspected of being typhoid fever. If the fever is at first marked by afternoon exacerbations with gradual rise,

and is followed in a few days by a more continuous fever, with persistent abdominal symptoms and a stuporous condition, if the spleen becomes palpable and rose spots appear, the diagnosis becomes more assured. A recent history of excursions away from home, contact with known cases of the disease, and no history of a previous attack of typhoid aids in determining the diagnosis. Although the diagnosis on symptomatic grounds is relatively easy in certain cases, it may be very difficult in others, owing to a suppression or diminution of any or most of the cardinal symptoms, or, on the other hand, owing to the predominance of certain secondary symptoms, such as acute cholecystitis, bronchitis, otitis media, and the like.

As already mentioned, typhoid fever may easily be overlooked in the beginning and in mild or abortive cases, particularly in children. It may readily be mistaken for other acute infections, as, for example, influenza, typhus, acute articular rheumatism, acute endocarditis, malaria, in proper localities for Malta fever or for relapsing fever, and for certain forms of tuberculosis.

Without futher emphasis on the purely clinical aspects of typhoid we may proceed to the methods of laboratory procedure without which no diagnosis should be made and in the absence of which no certain positive diagnosis can be asserted. We may go even further and state that if repeated and complete laboratory tests for typhoid fever, properly performed, result negatively, no definite positive diagnosis of typhoid fever should be made on the basis of the clinical examination alone.

The laboratory diagnosis of typhoid fever is made in one of two general ways: by detection of the typhoid bacillus in the body of the patient, or by determination of specific reactions produced in the body as a result of the infection.

DETECTION OF THE TYPHOID BACILLUS IN THE BODY

We have discussed the distribution of the typhoid bacillus in the body during the course of the fever to which it gives rise in considerable detail in the preceding chapter. We have seen that its distribution is general, that it may be found in the mouth, throughout the gastro-intestinal tract, in the urine, in the lymphatic system, in the gall bladder, and in all parts of the body reached directly or indirectly by the blood stream, which serves to disseminate it. The microorganism occurs, moreover, in the various complications of the disease, such as pneumonia and abscess formation, which it produces alone or in conjunction with

other bacteria. The typhoid bacillus may, then, at some period in the course of the disease be found in practically any given part of the body, but, as we have seen, its localization varies to some extent during the evolution of the disease. There are, as we have noted, certain foci of predilection for the typhoid bacillus, the bone marrow, bile, blood, and general lymphatic system in particular, in which places the bacteria are not only more constantly present but present in larger numbers. Success in detecting the typhoid bacillus depends, then, on choosing material that contains the micro-organism in considerable numbers and that is easily obtained. Typhoid bacilli are most readily isolated from the blood, bile, feces, or urine, and the reliability of each of these sources varies in accordance with the stage of the disease and with the individual case. Success further depends in large measure on the technic employed.

Isolation of the Bacillus from the Blood

We have indicated the difficulties that were met with by the early observers in obtaining positive cultures of the typhoid bacillus from the blood. The early failures were due in part to the fact that very small amounts of blood were used, frequently taken from the tissues surrounding a rose spot, and that small quantities of media or unsuitable media were employed. With more modern methods it appears that blood cultures are positive in approximately seventy-five per cent of all typhoid cases, success depending to a considerable extent on the period in the course of the disease at which the cultures are taken.

Blood for cultures is usually obtained from one of the veins just below the elbow joint, preferably from the median basilic, an engorgement of the vessel having been produced by a tourniquet applied to the lower part of the upper arm. In children or obese persons it may be very difficult to find this vessel, in which case blood may be obtained from the internal saphenous vein as it crosses over the internal malleolus, or in the case of children from the external jugular. In adults it may be necessary to dissect down on the vessel of the arm under local anaesthesia, in order to obtain a culture. The area through which the puncture is to be made is carefully sterilized, either by scrubbing with soap and water followed by bichloride and alcohol, or simply by the application of tincture of iodine, which prepares the skin rapidly and completely. In very sensitive individuals it may be wise to infiltrate the subcutaneous tissue with novocaine before inserting the needle. The blood is removed by means of a sterile, graduated

glass syringe, preferably of from ten or twenty cubic centimeters volume, and fitted with a needle of about eighteen gauge.

A great deal of the success in obtaining positive blood cultures depends on the amount of blood employed. In severe cases where the organisms are present in large numbers in the circulation, a few drops of blood may suffice to give positive results, but the majority of modern observers employ considerable amounts, usually ten cubic centimeters. The needle is inserted in the direction of the venous circulation, and with gentle suction a sufficient amount of blood is readily withdrawn in a few seconds, if the vein has been properly entered. Liberation of the tourniquet and withdrawal of the needle usually leaves little or no leakage about the skin puncture, which should be covered for a few minutes with a sterile sponge, or, if desired, protected from the air by a collodion dressing.

Cultures are preferably made at the bed-side, the needle and the mouth of the flask containing the media being thoroughly flamed over an alcohol lamp before inoculation. There is ample time to make successful cultures before coagulation of the blood, but if for some reason it is desired to carry the blood to the laboratory before inoculating media, calcium oxylate or a citrate solution may be added in sufficient amounts by filling the syringe partially with one or the other solution before taking the blood.

Either solid or liquid media may be employed in making blood cultures, the latter being under usual conditions preferable, with the exception of those cases in which it is desired to obtain a quantitative estimate of the number of bacteria to the cubic centimeter of blood. Solid media also have the advantage of economy of material and space, which in diagnosis in the field during war, and under similar imperfect laboratory conditions, may be a matter of importance. The use of poured plates of a mixture of agar and blood was first suggested by Schottmuller in 1900,[2] and they are still used, not only for the quantitative purpose just mentioned, but also for rapid differential diagnosis between typhoid and paratyphoid infections. For example, Koenigsfeld has recently recommended the addition of one cubic centimeter of blood to a slant agar tube containing Endo or Drigalski medium, in the latter case employing mannite instead of the usual lactose. Bile is added just before this medium is employed. Koenigsfeld obtained a high percentage of positive results and has been corroborated by Schurmann, who has somewhat modified the culture tube employed.

The majority of observers prefer to use a liquid medium, usually

alkaline bouillon or peptone water. Best results are obtained by using relatively large amounts of blood, usually ten cubic centimeters and about two hundred cubic centimeters of media in an Erlenmeyer or Florence flask. This considerable dilution of the blood prevents coagulation and checks the bacteriolytic activity of the serum, as was first demonstrated by Castellani [2] in 1899. Coagulation may also be prevented by the use of citrate solution, or better still, by the common method of adding bile, which not only prevents coagulation but is a selective medium for the typhoid bacillus.

The value of bile in cultures from typhoid cases was first pointed out by Conradi, who used a mixture of pure bile and glycerine and added small amounts of blood. This method was perfected by Kayser, who omitted the glycerine and used two and one-half cubic centimeters of blood to five cubic centimeters of sterile bile. This method, in addition to the advantage of using small amounts of blood, apparently gives a very high percentage of positive results, to judge from the numerous references cited by Kutscher. The diagnostic result, however, is arrived at less rapidly than when large amounts of liquid media are employed. Streaks are made on lactose, litmus agar two or three days after the growth in bile, and the organisms then carried further for final identification. According to LeBoeuf and Braun, sterile urine may be used in place of bile with equal success.

The culture method which we personally prefer and which is most generally employed consists in the addition of ten cubic centimeters of blood to two hundred cubic centimeters of ten per cent bile bouillon. Positive results run high, as we shall presently discuss, and in the majority of instances smears made from such a culture on the following day show Gram-negative bacilli in the positive cases. A not inconsiderable number of cases, however, will show no organisms for two or even three or four days. The diagnosis may be obtained more rapidly by making smears on agar from the bile bouillon after its incubation for from six to twelve hours.

Whereas the bile broth cultures or the pure bile methods are most certain for eventual diagnosis and in detecting the smallest number of bacteria, it is frequently desirable to estimate the number of organisms present in a given volume of blood, particularly in severe cases, where they are numerous. In this case solid media must be employed, and cultures obtained by mixing melted agar with a measured amount of blood. In the majority of cases it is difficult to obtain sufficient colonies with one or even

two cubic centimeters of blood if a single plate is made. In severe cases, however, a considerable number may be obtained from this volume. Landsberger has found as many as one hundred colonies in two cubic centimeters in the severe and hopeless cases. Both Jochmann and Schottmüller have used this method as indicative of the prognosis, and we have employed it to a limited extent in estimating the effect of vaccine therapy. We have further found that cultures from the blood clot are advantageous in estimating the number of organisms in a given amount of blood. By using a weighed amount of clot, which is then ground with bouillon in a sterile mortar, variations in the number of bacteria may be determined from day to day. Cultures from blood clots were first suggested by Fornet in 1906 and subsequently by Muller and Graef and by LeBoeuf and Braun. This clot method has the additional advantage of requiring only small amounts of blood, of obviating the necessity of immediate cultures at the bed-side, and of yielding serum which can be utilized for agglutination tests. Blood cultures in cases of typhoid are rarely contaminated when properly taken, and only in the very exceptional instances of mixed paratyphoid-typhoid infection do they show the presence of more than a single organism. The presence of Gram-negative, actively motile bacilli in the culture from a suspected case is presumptive evidence of typhoid or paratyphoid fever, but no diagnosis is complete until the organism has been isolated in pure culture and identified by cultural methods and agglutination tests. It should be noted in this connection that freshly isolated strains of the typhoid bacillus at times fail to respond characteristically to an antityphoid serum until they have been subcultured on artificial media.

The demonstration of the typhoid bacillus in the circulating blood is the most convincing evidence of typhoid fever and is free from even the few possible exceptions that must be made in drawing conclusions from the agglutination test. In addition, blood cultures are positive in nearly as high a percentage of cases as the agglutination test. Blood cultures have the further great advantage of being most frequently positive in the first week of the disease, at which time the Widal test is frequently negative. In view of the importance of early diagnosis, this fact is of great significance. The relative percentages of positive results from blood cultures have naturally varied markedly in the evolution of the methods which we have endeavored to outline. One hundred per cent of positive results, not only in the first week but at any time during the course of the disease, has been claimed by some

observers in a limited number of cases. It is certain, however, that on the average no such perfect success can be expected. In the following tables (Tables VII and VIII) we summarize considerable and recent statistics which show the results that may be expected from blood cultures at different stages in the course of typhoid fever. The data of Coleman and Buxton in these tables summarize the results in 1602 cultures based on the entire available literature and their personal experience. Our own results, as well as those of Mann, Rainsford and Warren, are based entirely on personal observations.

TABLE VII

PERCENTAGE OF POSITIVE BLOOD CULTURES IN CASES OF TYPHOID FEVER

		Per Cent Positive	*Per Cent on Repeated Cultures*
Coleman & Buxton collected results	1602 cultures	75%	—
Mann, Rainsford & Warren	391 cases	77%	—
Gay	98 "	71%	87%

TABLE VIII

PERCENTAGE OF POSITIVE CULTURES IN RELATION TO TIME OF DISEASE

	1st wk.	*2d wk.*	*3d wk.*	*4th wk.*	*After 4th wk.*
Coleman & Buxton	89	73	60	38	26
Mann, Rainsford & Warren	80	62	50	36	—
Gay	73	80	53	40	33

It will be seen from Table VII that the percentage of positive cultures by similar methods differs very little in the hands of these three observers. It is not certain whether the results of Mann, Rainsford and Warren and of Coleman and Buxton were based on repeated examinations in each given case or on a single examination, the latter being the probability. We have, therefore, added in our own cases the percentage of positive results on initial examination and the increased percentage obtained when more than one examination was made. The latter figure, of course, represents results that should be available in the diagnosis of any given case. It is evident, then, that a positive diagnosis may be expected from blood cultures in from seventy-five to eighty-five per cent of all cases of typhoid fever.

In Table VIII is found an expression of the experience of practically all observers who have taken any considerable number of

cultures in cases of typhoid fever. It will be seen that the number of positive cultures diminishes from the first week, or perhaps the early part of the second week, as judged from our own figures, onward. The high percentage of cultures we obtained in the second week may be due to the inevitable uncertainties in estimating the day of the disease correctly. In addition to these tables, a number of observers have found that blood cultures in the relapses of typhoid are usually positive. Coleman and Buxton, for example, list cultures from relapses in thirty-three cases, of which ninety per cent were positive. Clarke obtained thirty-seven positive cultures out of forty-six cases (eighty per cent).

Whereas cultures are more likely to be positive in the early days of typhoid fever, agglutination reactions are more frequently positive later in the course of the disease, as we shall see at a later point. These facts, which are undoubted, give the impression that there must be some relation between the two results. It is convenient and probably correct to think of the course of typhoid fever as representing a balance of forces between the invading agent and the resisting host. It seems certain that the building up of antibodies postulates the disappearance of bacteria and that recovery is finally due to their complete destruction, at least in the circulating blood. A careful analysis of the strength of the Widal which we have estimated in a large number of cases, however, fails to show any direct relation between its potency and the presence or absence of positive blood cultures. On the other hand, we do find with Schtulern that a sudden jump in the Widal titer is usually coincident with the disappearance of the bacteremia. This is particularly true in cases that have been treated by intravenous injections of vaccines, where such an occurrence often takes place in conjunction with the characteristic reaction produced by this type of therapy. The disappearance of bacteria from the blood has also been shown by Ghenken to be coincident with the disappearance of the Diazo reaction, one of the diagnostic signs in typhoid, which we shall consider later.

Isolation of Bacillus Typhosus from the Stools

A. Pfeiffer in 1885 showed that typhoid bacilli are present in the stools of cases of typhoid fever. We have discussed, in the last chapter, the distribution of the typhoid bacillus in the gastro-intestinal canal, which affords the channel of entry into the body. We know that the original infecting dose of typhoid bacilli is absorbed from the intestinal canal into the lymphatic system, but the bacillus subsequently reappears in the intestine, owing to its

elimination in large numbers from the gall bladder. As we have already stated, the organism is present in the intestine in largest numbers relatively late in the disease and occurs both in larger numbers and in greater purity in the upper parts of the intestine. In the lower levels it is not only mixed with, but actually inhibited or killed by overgrowth of the colon bacillus. It appears also that a carbohydrate diet decreases the number of typhoid bacilli and increases the number of colon bacilli. At all events, the typhoid bacillus is less readily isolated from the stools than from the blood, owing to the admixture of other bacteria. Isolation of the bacillus from the stools is not so important a procedure in the diagnosis of typhoid fever as it is in the detection of typhoid carriers, and it is chiefly from the latter standpoint that the most extensive investigations have been made.

Typhoid bacilli are more readily found in fluid than in solid stools, either during the course of the disease or in convalescence. It is usually preferable to dilute the stools and to allow them to stand and separate out, subsequently seeking the microorganism in the upper and more fluid part. Inasmuch as the organism is present in larger numbers in the duodenum, various cathartics have been employed to bring down the contents of the upper bowel rapidly. Elaterin has recently been employed by Tonney, Caldwell and Griffin with great success for this purpose in a series of suspected carriers. A very great number of methods and media have been described for the isolation of the typhoid bacillus from its admixture with other organisms in the feces. The difficulty of isolation is increased by the fact that there is, strictly speaking, no medium which may be employed for the enrichment of the typhoid bacilli at the expense of the other bacteria which are usually present in predominating numbers. Schmitz [2] has claimed that the addition of beef serum to media will accomplish this purpose. The addition of an agglutinating antityphoid serum has been used to collect a few typhoid bacilli that may be present in contaminated water, and thereby to facilitate their isolation. In a converse manner Landmann has added an anticolon serum to dilute stools; after standing and centrifugalization, the supernatant fluid is injected into the peritoneal cavity of a guinea pig. The exudate, removed thirty minutes later and plated, gives a pure culture of Bacillus typhosus. But, in general, the methods of isolation depend on the relatively greater resistance of the typhoid bacillus to certain harmful substances and on certain minor biological peculiarities of its growth. We have already discussed the biological properties of Bacillus typhosus, which serve to

differentiate it from Bacillus coli and which may be used, therefore, in the isolation of the specific microorganism. The isolation of the specific microorganism may be effected either in one or in two stages by means, first, of a preliminary treatment designed to inhibit or destroy other organisms, and, secondly, by the plating methods which serve to differentiate separate colonies of typhoid from other colonies, either directly from the stools or after they have been subjected to the preliminary inhibiting treatment.

The means of inhibiting the growth of other bacteria and thereby enhancing the possibilities of finding the typhoid bacillus depend on the biological peculiarities that we have already discussed. Among these may be mentioned, first of all, the greater motility of the typhoid bacillus, a fact which is made use of in the sand tube and general filtering methods that have been mentioned. More important, however, is the employment of various chemical substances which inhibit the growth of streptococci and colon bacilli in particular and leave typhoid bacilli relatively unaffected. The most important of these are malachite green, brilliant green, crystal violet, caffeine, and more recently petrol ether, the action of all of which materials we have discussed in detail.

Typhoid bacilli may be found in the stools with or without preliminary treatment by making smears over the surface of prepared plates. A sterile glass rod is dipped in the fluid and often diluted stools and smeared over the surface of a succession of plates without re-inoculation. The most important media employed in preparing these plates are the Conradi-Drigalski medium, containing lactose, litmus, nutrose and crystal violet, and Endo's medium, containing lactose, basic fuchsin and sodium sulphite. On such surfaces the colonies of typhoid bacilli are differentiated from those of colon bacilli by their failure to produce acid. Suspected non-acid colonies are then tested further on one or more of the various differentiating media, such as Russell's medium, Congo red, neutral red or subacetate of lead, as well as the ordinary media such as litmus milk and various differential sugars. They are then finally tested for their agglutinability by a typhoid immune serum.

The detection of typhoid bacilli in stools depends a great deal on the skill of the individual investigator and his employment of a medium to which he is accustomed. The percentage of positive results, moreover, varies in accordance with the stage of the disease, for reasons that we have fully discussed. The microorganism may be demonstrated in a very high percentage of cases under proper conditions. Klinger, for example, was able in 3214 ex-

aminations to find Bacillus typhosus in eighty-one per cent of all cases. Hiss,[2] who was one of the earlier observers, found typhoid bacilli in the stools in a little over ten per cent during the first ten days of the disease, in fifty per cent from the eleventh to the twentieth day, and in over eighty-one per cent from the twenty-first day on. Recent comparative results of various investigators in obtaining typhoid bacilli, arranged in accordance with the week of the disease, are illustrated in Table IX.

TABLE IX

PERCENTAGE OF POSITIVE CULTURES FROM STOOLS IN SUCCESSIVE WEEKS OF TYPHOID FEVER

	1st wk.	*2d wk.*	*3d wk.*	*4th wk.*	*Total No. Cases*
Brion & Kayser	32	35	45	—	144
Bohne	0	23	43	100	27
Gaehtgens & Bruckner	57	53	77	50	100

Isolation of the Typhoid Bacillus from the Bile

The early and continued localization of typhoid bacilli in the gall bladder and bile has been much insisted on. The constant presence of the organism in this locality has suggested the possibility of its isolation for diagnostic purposes from this source. The only difficulty in this method lies in obtaining the bile, and this is possible by one of two methods, either by an oil meal or by intubation. In the first case 100 to 200 cubic centimeters of olive oil are given on an empty stomach, removed from the stomach after an hour or two, and found to contain a considerable admixture of bile. Kiralyfi was able to obtain the typhoid bacillus from bile obtained in this manner in cases that failed to show the organism in the blood or feces, and a number of other authors (e. g., Carnot and Weill-Hallé) have also used this method with some success as accessory to feces examination.

The other and now more usual method of obtaining bile is by the use of Einhorn's duodenal sound as employed by Hess as early as 1912, which yields within a few hours on aspiration considerable amounts of pure bile.

Our own experience with cultures from the bile in a limited series of cases leads us to believe with Purjeesz and Stepp that cultures are rarely positive when the feces are negative, although it unquestionably gives an additional method of diagnosis, particularly in the case of carriers, and, apart from the difficulty in obtaining material, gives an easier method of isolating the organism than from the feces. As examples of the success in mak-

ing bile cultures, it may be noted that Reading obtained thirteen positive results out of eighteen in cases of typhoid, and Kaspar found typhoid bacilli in the bile seven years after recovery from the disease.

Isolation of Typhoid Bacilli from the Urine

One of the metastatic foci of typhoid bacilli in the body during the course of the disease is the kidneys. Small nodules of bacteria were histologically demonstrated in this locality by Konjajeff in 1889, and had been isolated from the urine by Hüppe three years previously. Petruschky in 1898, pointed out the importance of the urine from typhoid cases and during convalescence as a means of spreading the disease. When the organism is present, it is relatively easy to detect, owing to the fact that it is usually in pure culture. It occurs in twenty-five to fifty per cent of all cases, and probably more frequently when albumin is present in the urine. Its appearance in the urine is, as in the case of the stools, more likely from the second or third week onward. Enormous numbers of bacteria may be present, as many as thirty to one hundred millions to the cubic centimeter. It is said to occur coincidently with the appearance of the roseola on the surface of the body, which is simply another metastatic focus. The presence of the microorganisms in the bladder under usual conditions gives rise to no distinctive symptoms, although it may lead after convalescence to severe cystitis.

Among other sources that may be mentioned for obtaining typhoid bacilli from the body as a means of diagnosis in typhoid fever are splenic pulp obtained by puncture, pus from localized complications, the sputum during the disease, and smears from the throat and tonsils. These sources are much less reliable than the ones that we have discussed more fully, and, in the case of the splenic pulp at least, offer so grave a danger in securing material as to make it impossible to recommend the method.

THE DIFFERENTIAL DIAGNOSIS OF BACILLUS TYPHOSUS

Suspected colonies of typhoid bacilli are taken in subculture from blood, stool, urine or bile specimens that have been plated or smeared on solid media and further examined. A simple smear on agar may be made in the case of blood cultures where the growth is obviously a pure one. Such pure cultures are then further studied and identified as typhoid bacilli in accordance with accepted cultural characteristics and by means of agglutination

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tests. Certain of the preliminary steps in the determination are usually made during the process of isolation, particularly when selective sugar media serve to separate non-acid-forming colonies from colon bacilli. Any organism to be a proved typhoid bacillus must fulfil at least the essential characteristic tests, which are briefly as follows:

The organism is a Gram-negative, motile bacillus, which produces very slight acid and never coagulation in litmus milk, produces acid in glucose media without gas, and no change in lactose or saccharose. It produces no indol in peptone water or bouillon and no change in neutral red agar.

In addition to the cultural characteristics, the ultimate and necessary proof of an authentic typhoid bacillus lies in its specific response to antityphoid serum. A diagnostic serum of this sort is produced by the immunization of animals, usually rabbits, horses or goats, by repeated injections of one or several authenticated typhoid strains. The serum of known typhoid cases may in some cases be employed in the diagnosis of suspected bacteria. An artificial immune serum for diagnostic purposes should be able to clump laboratory strains of typhoid in dilutions of one to 5,000 or more, and any suspected typhoid bacillus should respond characteristically up to or very nearly to the titer limit of the serum. Difficulty is at times met with, however, in certain recently isolated strains of bacilli which fail to respond in a characteristic manner. This inagglutinability of recently isolated strains of the typhoid bacillus, as first noted by McWeeney, is of interest in its general bearing on the problem of pathogenicity and variations in antigenic properties in a given species. It seems undoubted, not only that individual strains of bacteria of a recognized species differ in their properties of producing disease, but, further, that pathogenic properties disappear through the residence of a microorganism in artificial culture media. Although with many organisms, including the typhoid bacillus, it is not possible to demonstrate such loss of pathogenicity since we know even old laboratory cultures may produce human infections, with certain other bacteria, as, for example, staphylococcus and streptococcus, such loss in pathogenicity after isolation from the body is very evident. There is, on the other hand, evidence that the growth of typhoid bacilli in the body, in immune serum, or on blood media renders them more resistant to the action of serum and probably to the protective power of the body. Patrick has shown that cultures isolated early in the course of the disease agglutinate better than those during later stages, and those from

the stools better than organisms obtained from the blood. In other words, growth in the blood tends to render the organism less susceptible to the action of a specific serum than organisms that have been out of the body for some time. Sick has shown that typhoid bacilli grown on blood media are less agglutinable. In general it has been found that fully virulent typhoid bacilli are less agglutinable than avirulent strains (Fornet [2]). Minor variations in agglutinability may be produced by simple variations in the culture medium, as, for example, increasing the amount of alkali (Wassermann), or by the use of malachite green (Lentz and Tietz). This whole question has been studied by Gay and Claypole,[2] owing to an interesting observation made in connection with studies on the carrier conditions in rabbits. It was found that typhoid bacilli that had been long resident in the rabbit body and had been grown outside the body on media containing rabbit blood became wholly inagglutinable by a strong (titer 1 to 20,000) antityphoid serum, produced by immunizing rabbits against ordinary stock cultures of the same organism. It was found, however, that when a serum was produced by immunizing rabbits with blood agar cultures of the same strain of the typhoid bacillus, the blood strain was readily agglutinated. These observations are not only of theoretical interest but of practical importance in the diagnosis of strains of typhoid bacilli. Gay and Claypole found that such an antiserum to blood strains of typhoid bacilli would agglutinate recently isolated strains of typhoid bacilli, which were either only feebly or not at all agglutinated by the ordinary diagnostic serum.

DIAGNOSIS OF TYPHOID FEVER BASED ON SPECIFIC REACTIONS ON THE PART OF THE PATIENT

Typhoid infection produces reactions in man which are more or less specific, which may be demonstrated by methods of laboratory precision, and are of great value in diagnosis. These reactions may be grouped under four general headings: serum reactions, reactions of localized hypersusceptibility; metabolic reactions, as demonstrated by certain chemical changes in the body; and, finally, reactions on the part of the leucocytes.

Serum Reactions

The reactions evidenced by changes in the blood serum are among the most characteristic, specific and diagnostically valuable signs of typhoid fever. Of these reactions the most important

is that of agglutination. The phenomenon of agglutination was first observed by a number of French investigators, Charrin and Roger, Metschnikoff, and Bordet in particular, before its diagnostic significance, particularly as evidenced in typhoid infections, was appreciated. This reaction depends on a specific property which appears in the serum of an animal that has been infected or artificially immunized against any particular microorganism. This property is evidenced by the rapid agglomeration of suspensions of the causative microorganism produced by addition of the specific serum in question, even in minute traces. In the case of the typhoid bacillus the utilization of this reaction in diagnosis was preceded by observations on the part of Gruber and Durham, and by Pfeiffer and Kolle,[2] who commented independently on the properties that typhoid immune serum has of immobilizing and clumping the typhoid bacillus. The utilization of this fact in the diagnosis of typhoid was undoubtedly first appreciated by Grünbaum [2] in Nothnagel's clinic, although he failed to record his observations until after the publication of a limited series of cases by Widal, who had independently obtained the same results. This diagnostic method depends on the more or less specific power which the serum of typhoid patients has of agglutinating typhoid bacilli.

The methods which are employed in carrying out the agglutination test in typhoid have changed remarkably little since Widal's description, owing to its relative simplicity. Material from the patient may be obtained either by allowing a few drops of blood to dry on a glass slide or other impervious surface, or, somewhat better, by obtaining a small amount of blood and allowing it to clot in a tube, in which case the expressed serum is utilized. Diagnosis by means of serum is distinctly more accurate in point of view of dilution used, and the obtaining of serum for this purpose sufficiently simple to be expected of the general practitioner. A series of dilutions are made either by dissolving the dried blood in salt solution or distilled water, or by using a measured amount of blood serum; and to each of this series of dilutions, as well as to a control tube containing salt solution, is added the same measured amount of typhoid bacilli. The typhoid bacilli employed may be either in the form of fresh, living bouillon cultures or agar cultures freshly suspended in bouillon, or else cultures killed and preserved by the addition of formalin (0.1%). The use of living cultures is somewhat more general and has the advantage of illustrating the two successive phases in the reaction, namely, a loss of motility on the part of the typhoid bacilli and their subsequent

clumping. It has, however, the disadvantage of requiring daily preparation, offering dangers of infection, and affording a less uniform reagent for the test. The choice between these two preparations of the typhoid bacillus, again, is somewhat dependent on the method by which the dilutions and the reaction in general are carried out. There are two general methods that are employed, the microscopic and the macroscopic.

The microscopic method requires smaller quantities of blood and is carried out by making dilutions by the drop method with the addition of bouillon or salt solution to the serum. Each of these dilutions is then mixed with an equal amount of the culture or preparation of the typhoid bacillus on a glass coverslip, which is inverted and sealed with vaseline over a hollow ground slide. Such preparations when observed at intervals soon show a loss of motility on the part of the living bacteria and their aggregation in small clumps. The reaction should be complete within an hour to be diagnostically positive, and frequently occurs in a few minutes.

The macroscopic method is distinctly more accurate in point of view of dilution of the serum, and, therefore, measures the actual potency in agglutinins of any given serum. Personally, we recommend this method not only for accurate scientific work in which it is absolutely necessary, but for diagnostic purposes as well. Small amounts of serum are carefully measured either by means of a graduated pipette or by the drop method, and usually so arranged that the given dilution is available in a volume of one cubic centimeter. A series of dilutions of this sort is then arranged in test tubes and to each dilution the same amount of a living or formalin killed culture is added and the mixture carefully shaken. The result of the test performed in this manner is judged by the complete sedimentation of all the bacteria as read on the following day, with coincident clarification of the supernatant fluid. The macroscopic method is clearly positive or negative, and gives no pseudo reactions, such as loss of motility with partial clumping, as may confuse the diagnosis when the microscopic method is followed. In an extended experience we have also found the use of formalin killed cultures of greater delicacy and accuracy for diagnostic purposes than when living cultures are employed.

A standard culture of the typhoid bacillus should be consistently employed in diagnostic tests. This culture should be chosen in accordance with its ready and unvarying agglutinability under ordinary conditions of culture.

Another modification of the agglutination test has been suggested by Mandelbaum,[2] and depends on the phenomenon of agglutination in threads rather than clumps, as previously described by Pfaundler. Mandelbaum found that bouillon cultures of the typhoid bacillus, allowed to grow for several hours at 37° with admixture of serum from a typhoid patient, tend to grow in chains which are characteristic and which do not occur when the organism is grown in the serum of non-typhoidal cases. This thread reaction of Mandelbaum's has since been obtained by other observers (Gaethgens and Kamm; Ast) and found to be somewhat more delicate than the ordinary agglutination test in point of dilution, and possibly of earlier diagnostic significance. It has not, however, been generally adopted.

The determination of the degree of dilution that is diagnostically positive in typhoid is of great importance. Widal originally thought the reaction diagnostically positive when present in a dilution as low as one to ten. It has since been shown that the sera of normal individuals may give such a reaction, at least when the microscopic method is followed, and the ordinarily accepted standard for a positive reaction is one to forty or one to fifty, at which dilution normal serum has been found rarely or never to react. From our personal experience with formalinized cultures we find that a dilution of one to forty may certainly be accepted as positive, and positive reactions of one to twenty or even of one to ten are only in the rarest instances present in normal individuals or in those suffering from other diseases when the macroscopic method is employed. Thus, in sixty-seven non-typhoidal cases which we studied in connection with a larger series of proved typhoid cases, a positive agglutination test was obtained at a dilution of one to ten in only three (4.5 per cent), and in at least two of these individuals a previous history of typhoid could certainly not be excluded. A dilution, then, of even one to ten is with our method very suggestive. The strength of the dilution varies considerably in individual cases and during the course of any given case. In general, it is found to increase after its initial appearance, although it may fluctuate markedly, and at times, after becoming positive, disappear. A reaction in a dilution of one to three hundred or four hundred is in our experience common, and it has been obtained as high as in a dilution of one to 163,840 (Kleinberger). We are inclined to attach some significance to the strength of the Widal in relation to the prognosis. In general, it would seem that a strong Widal indicates a more successful resistance and gives better promise of the outcome. It certainly bears some relation

to the results obtained with vaccine therapy, as we shall see in a later chapter.

The agglutination test, whereas highly accurate and valuable in the diagnosis of typhoid fever, is by no means absolute. It is open to several causes of error which may militate against its unequivocal acceptance in any given case. A negative result is certainly not proof of the absence of typhoid fever, owing to the lateness in the appearance of the reaction in many cases. On the other hand, a positive result is highly indicative of typhoid fever, with certain exceptions. The most important of these exceptions lies in the case of suspected typhoid fever in an individual that had been vaccinated against the disease. Such individuals as a result of vaccination show agglutinins in their blood serum under ordinary conditions, at least for several months. In such a given case the diagnosis of typhoid fever, which may occur in spite of the prophylactic treatment, is difficult. We shall discuss it more fully in connection with prophylactic immunization, but it may be stated here that a positive diagnosis is probable even in these cases when an originally positive Widal in low dilutions increases coincidently with a suspected fever. It has also been claimed by Seiffert and by Dawson that vaccination against typhoid does not produce a group agglutinin for Bacillus enteriditis (Gaertner), whereas the serum of typhoid cases does contain such a minor agglutinin. Another possible error in diagnosis lies in the occasional failure of the test to differentiate between typhoid and paratyphoid fevers. The serum of a paratyphoid fever case will under certain conditions agglutinate the typhoid bacillus as well as the paratyphoid bacillus responsible for the infection. The error in diagnosis, although not a serious one, militates against the absolute specificity of the reaction. In general, it is found, however, that the reverse is more likely to be true; that is to say, the serum of a typhoid case may agglutinate the paratyphoid bacillus, particularly Paratyphosus alpha, as well as Bacillus typhosus. When the Widal is low, say in a dilution of one to fifty, it is possible that the typhoid bacillus may be agglutinated in higher dilution than the paratyphoid bacillus in a case of paratyphoid fever. When, however, the reaction to the typhoid bacillus is high, say one to two hundred, it is not likely that the infection is anything other than straight typhoid fever. The possibility of a double infection due to the typhoid bacillus and one of the paratyphoids should be kept in mind. Such infections have been bacteriologically proven by blood cultures. At all events, the differential diagnosis may be possible in anomalous group reactions of this

sort by utilizing the absorption method of Castellani, which serves to differentiate between major and minor agglutinins, and thereby to indicate the organism which is really giving rise to the infection in question. A description of this method will be found in many modern text-books on bacteriology and immunology.

As indicative of the value of the agglutination reaction in the diagnosis of typhoid fever, we present in the following table comparative recent results with the agglutination test. This table shows not only the percentage of cases which give a positive agglutination test at some time during the course of the disease, but also indicates the expectation of positive diagnoses at different stages.

TABLE X

RECENT ESTIMATES OF POSITIVE AGGLUTINATION REACTIONS IN TYPHOID FEVER IN SUCCESSIVE WEEKS

	1st wk.	*2d wk.*	*3d wk.*	*4th wk.*	*5th wk.*	*Average*
Park and Williams	20	60	80	90	—	88
Tanaka	70	—	86.4	100	—	——
Gay	61	82	87.5	92	100	91.8

It is evident from this table that a positive agglutination test may be expected in about ninety per cent of all cases, and that the success in obtaining a positive result increases very markedly from the second week onward, until it is positive in nearly all cases by the fourth week.

A number of other serum tests have been suggested for typhoid fever. They are all of interest as indicating the nature and degree of the reaction produced in the human body by typhoid infection, but none of them approach the agglutination test in reliability for diagnostic purposes. They may, therefore, be very briefly summarized.

Fixation Reactions in Typhoid

Typhoid fever was one of the conditions in which Bordet and Gengou were able to demonstrate the presence of sensitizing substances by means of their now famous reaction of alexin fixation. These authors found that if the serum from a convalescent case of typhoid fever is mixed with the typhoid bacillus, it acquires a new property, due to some change in its colloidal complex, of fixing the reactivating substance of fresh serum, known as alexin or complement. The occurrence of this reaction in typhoid cases led Widal and Le Sourd to test it out as a diagnostic method. They found it

present in fifty-nine out of sixty-one cases, and similar results have frequently been obtained by others. There is no question but that at some time in the course of the disease a fixation reaction may be demonstrated. Its appearance, however, is delayed even longer than the agglutination reaction, and it does not ordinarily occur before the second or even the third week (Hage and Koriff-Petersen). The reaction is most successful when carried out with a polyvalent antigen, which again suggests the multiplicity of bacterial strains that may be responsible for typhoid fever. Garbat has recently found that the fixation reaction is not so likely to occur following immunization against typhoid as it is during the course of typhoid fever. Its presence, therefore, is of some diagnostic value in suspected typhoid fever in vaccinated individuals.

The Bactericidal Property of the Serum of Typhoid Patients

Stern and Korte have suggested a test which has been used to a limited extent in diagnosis. They found that if the heated serum of typhoid cases in very considerable dilution, in some cases as great as one to 50,000, is added to a mixture of living typhoid bacilli and rabbit alexin and incubated, plates made at intervals will subsequently show destruction of the organism. No such destruction is produced by the serum of normal individuals or of other cases. This reaction is important as indicating an increase in bacteriolytic antibodies in the course of typhoid fever, but has been found generally of less reliable diagnostic value than the agglutination test.

Tropins and Opsonins in Typhoid Serum

It may be definitely accepted (Fornet [2]) that the opsonic index or tropin titer of the serum of typhoid cases almost invariably exceeds that of normal individuals, reaching frequently 1.5 to 2.5. Miss Smith in our laboratory has confirmed this finding. The complexity and uncertainty of the technique, however, render this test of little value as a diagnostic procedure.

Among other serum tests which have been suggested in typhoid are the demonstration of a typhoid precipitinogen, shown by adding a strong antityphoid serum to the serum of a case of typhoid fever (Fornet [3]); the myostagmin reaction, depending on a change in surface tension when an extract of typhoid bacilli is mixed with typhoid serum (Ascoli); and the conglutination reaction (Gay and Lucas). None of these reactions have, however, been sufficiently worked with to merit further comment.

METHODS OF DIAGNOSIS DEPENDING ON EVIDENCE OF LOCALIZED HYPERSUSCEPTIBILITY IN THE PATIENT

Several tests have been proposed in typhoid fever, the success of which depends on the demonstration of the hypersusceptibility of the patient to the infecting agent. Among these may be mentioned the opthalmo reaction proposed by Chantemesse. This reaction is produced by dropping a small amount of fluid containing one-fiftieth of a milligram of powdered typhoid toxin in the conjunctival sac. A much more severe reaction is obtained in typhoid cases than in normal individuals. In fact, a serofibrous exudate is frequently produced. A number of attempts have been made to diagnose typhoid fever by the presence of a cutaneous or intradermal anaphylactic reaction. Such studies have been made by Wolff-Eisner, Link, Floyd and Barker, and Jeanneret. Such reactions may be demonstrable late in the course of the disease, but, owing to their tardiness in appearance, are of no considerable diagnostic value. A similar reaction has, however, been found by Gay and Force to occur in recovered typhoid cases and serves as an index of immunity to typhoid fever. Ascoli [2] has demonstrated a passive transfer of hypersusceptibility by injecting the serum of typhoid cases in guinea pigs that are subsequently given extracts of typhoid bacilli.

Vincent has described a characteristic reaction in the spleen in cases of typhoid fever, when the individual is given an injection of two cubic centimeters of autolysate obtained from typhoid bacilli. In response to such an injection, the spleen of the typhoid case may be demonstrably increased in size in from twelve to eighteen hours after inoculation.

DIAGNOSTIC REACTIONS DEPENDENT ON CHANGED METABOLISM IN TYPHOID FEVER

The prolonged course of typhoid fever is accompanied by marked destruction of the body proteins. This destruction is demonstrable in the patient's urine. During the febrile height of the disease the urine is decreased in amount, frequently contains albumin, and usually shows an increase of urea and uric acid, and a diminution in chlorides. Indican is present in large amounts and the toxicity of the urine for experimental animals is increased. A most characteristic reaction occurs in the urine in the course of typhoid, as was first pointed out by Ehrlich, which depends

probably on the abnormal decomposition of proteins in the body. This "diazo reaction," as it is called, is demonstrable by the addition of a diazo benzene sulphonic acid reagent in two solutions to the urine. A positive reaction is evidenced by a reddish color in the foam produced in the course of the reaction. A simpler substitute for the diazo reaction is the urochromagen reaction, produced by the addition of a dilute solution of potassium permanganate to diluted urine, which produces a bright yellow pigment in positive cases.

Both these reactions are usually present in typhoid fever cases. The diazo reaction has been estimated by Brouardel and Thoinot to occur in ninety-seven per cent of cases. Its absence, then, is of distinct diagnostic value, as indicating that the case in question is not typhoid. A positive reaction, however, is no certain criterion of typhoid fever, inasmuch as it has been found to occur in other febrile diseases, particularly in measles, scarlet fever, pneumonia, and erysipelas.

CHANGES IN THE LEUCOCYTE COUNT IN THE COURSE OF TYPHOID FEVER

We have already discussed the characteristic localization of the typhoid bacillus in the bone marrow and the degenerative changes produced thereby. This localization in the bone marrow is associated with characteristic changes in the white blood cells of the circulating blood. Whereas the majority of infectious diseases, particularly those associated with localized purulent processes, are accompanied by an increase in the polymorphonuclear leucocytes, typhoid fever, except in its very beginning, is usually associated with a diminution of these cells. The total leucocyte count during most of the course of the disease is diminished, owing to an absolute and relative diminution in the polymorphonuclear neutrophiles. This leucopenia may be preceded in the earliest days of the disease by a transitory hyperleucocytosis. The count during the greater part of the disease characteristically ranges from two thousand to four or five thousand. Eosinophiles are practically never found in active typhoid fever, and the large mononuclear cells are relatively increased. Intercurrent infections, such as pneumonia, may produce a slight rise in this leucocyte count, say to a count of ten thousand, which, however, would be distinctly below the count characteristic of an uncomplicated pneumonia. Convalescence and recovery are associated with a re-appearance of polymorphonuclear cells and

particularly of the eosinophiles. No direct relation between the degree of leucopenia and the prognosis is admitted by the majority of investigators. There does seem, however, to be a distinct relation between the relatively high leucocyte count or the artificial production of a high leucocyte count and a favorable prognosis. This point will be more particularly insisted on in connection with the chapter dealing with the treatment of the disease.

SUMMARY OF THE DIAGNOSTIC VALUE OF THE VARIOUS LABORATORY TESTS

In summary of this section, which deals particularly with the methods of laboratory diagnosis in typhoid fever, it may again be stated that no diagnosis of the disease should ever be made without laboratory aid. It is, moreover, doubtful whether a positive diagnosis of typhoid fever can be made in the absence of corroborative laboratory tests. Most important and reliable of these laboratory tests are the agglutination reaction and the demonstration of the typhoid bacillus in the circulating blood. Of less but still of distinct corroborative value are the diazo reaction, a total and differential leucocyte count, and the demonstration of the organism in the feces, bile or urine.

Blood cultures in the early stages of the disease and agglutination tests from the second week onward are alone or together positive in the great majority of cases. In combination the two tests are almost absolutely conclusive. Their presence certainly proves typhoid fever; their absence strongly indicates its absence. Our own personal results in laboratory diagnosis may perhaps be summarized as indicative of the diagnostic value of these two tests when systematically carried out. We have recently summarized our laboratory examinations in 194 suspected cases of typhoid fever. Many of these cases could subsequently be definitely shown to be not typhoid on the basis of purely clinical appearance. Thus, sixty-two of these cases in which the laboratory findings were negative were subsequently found to be some other disease on clinical evidence. In eight cases a clinical presumptive diagnosis of typhoid remained unchanged, and yet there was no laboratory evidence forthcoming to substantiate this diagnosis. A negative laboratory diagnosis means negative blood cultures and Widal, and subsequent to these examinations, negative findings in the stools and urine. If we are to admit, then, that these cases may have been typhoid fever in spite of

negative laboratory evidence, it would appear that the possible failures in diagnosis of real typhoid cases by laboratory methods would be approximately four per cent.

On the other hand, there were 124 cases in which the clinical and laboratory diagnosis agreed. Ninety-eight of these cases were treated by a type of vaccine therapy to be later described, and in them very careful and complete laboratory examinations were made. In these ninety-eight clinically typical cases of typhoid fever both the blood culture and the Widal were present in sixty-eight per cent. The blood culture was present in seventy-one per cent, and the agglutination test, taking a dilution of one to forty as a positive criterion, was present in 91.8 per cent. Either a Widal or a blood culture was positive in 97.3 per cent of the cases examined. A positive laboratory diagnosis in 2.7 per cent of the cases only depended on the demonstration of the micro-organism in the stools or urine alone.

CHAPTER VII

THE SEQUELS OF TYPHOID FEVER AND THE CARRIER CONDITION

Typhoid fever is a serious disease not only through its intrinsic and complicating dangers, but owing to the numerous untoward results which follow in its train. The continued proliferation of a parasite in every part of the body over a period of days and weeks with persistent high fever and profound toxic metabolic changes in every organ and cell exerts a fundamental influence on the health of the body as a whole. A bacteriological recovery from typhoid fever by no means predicates immediate or even ultimate restoration to a previous normal. Recovery, again, from the disease itself may either be accompanied by disappearance of the typhoid bacillus, or by its persistence in one or several metastatic foci. Such persistence is frequently non-symptomatic, as we shall see.

SEQUELS AFTER BACTERIOLOGICAL CURE

We may for convenience discuss the sequels of the disease in accordance with the persistence or disappearance of the typhoid bacillus from the body. In cases of bacteriological cure the disappearance of the bacillus from the blood and later from the residual foci follows, *pari passu*, the abatement and disappearance of fever. The disappearance of bacilli in appreciable numbers from the blood antedates a return to normal temperature by several days as a rule, but bacteria remain in certain parts of the body, gall bladder, intestine, and bone marrow in particular, for several days after permanent normal temperature, even in favorable cases. This persistence is evident clinically in the case of relapses, and in all probability by those slight exacerbations of fever which follow initial exertion or even excitement during the convalescent period. Complete convalescence is a matter of days or, in unfavorable cases, of weeks, after a normal temperature has been reached. A re-establishment of weight and strength requires time even in the most robust, but later in convalescence weight may be taken on more rapidly and in excess of the previous normal, when the metabolic functions of the cells have been slightly but not seriously injured.

In no inconsiderable percentage of cases recovery from active fever is followed by prolonged convalescence and debility. For example, Whittington in a recent series of cases found fourteen per cent in which recovery was abnormally slow. The debility which follows typhoid is usually not so evidently related to the illness that causes it, as in these cases we have mentioned; it is best shown by the greater susceptibility to other infections that is evident not only over a period of weeks but of years. Dublin, in statistics we have already quoted, has shown that death is more than twice as frequent in the three years following recovery from typhoid fever as under normal conditions. An increased susceptibility to tuberculosis is particularly evident. This fact was appreciated by the earlier clinicians and was especially emphasized by Bartlett.* Woodruff has demonstrated the predisposition to tuberculosis in typhoid recoveries by showing that the death rates from the two diseases follow similar curves in thirteen countries. In Dublin's study of the increased death rate that follows recovery from typhoid, 38.9 per cent of the deaths in the three following years were due to tuberculosis. Sedgwick and MacNutt found that coincident with the reduction of typhoid mortality through purification of water supplies the mortality from pulmonary tuberculosis decreases.

Frequent temporary and at times permanent affections of the central nervous system follow typhoid. In addition to meningitis and brain abscess, which are more properly complications of the disease, authorities mention various forms of insanity characterized either by mania or melancholia, hysteria, and also more evident structural modifications such as neuritis, multiple sclerosis, anterior poliomyelitis and paralyses, either in the form of paraplegia or of hemiplegia.

Derangements of the circulatory system are not infrequent sequels, and are in origin at least due to local deposition of bacterial nests, probably complicated by a slowing of the blood stream. Arteritis, phlebitis, and particularly venous thrombosis (phlegmasia alba dolens) are well recognized. Murchison mentions thrombosis of the femoral vein in one per cent of his cases, and Whittington found thrombosis in three per cent of his cases. It is known to persist or recur for years, but fortunately it rarely produces embolism. Gangrene is regarded by Keen, who has collected 115 cases from the literature, as a sequel in typhoid of no inconsiderable surgical importance.

* Loc. cit., p. 120.

TYPHOID SEQUELAE DUE TO PERSISTENCE OF THE TYPHOID BACILLUS IN THE BODY

The foregoing sequels that have been touched on are not intimately related to persistence of the typhoid bacillus in the body of the nominally recovered host. We are now to consider those far more important and numerically considerable cases of the disease which continue to harbor the microorganism for days, weeks, and at times for years after recovery from the fever. Such bacillus carriers are significant not so much from the standpoint of their own welfare as from the menace they offer in spreading the disease to others. Before proceeding to a detailed discussion of the real carriers and disseminators of typhoid infection, who generally themselves remain free from dangers of typhoid infection, we may first consider those recovered cases in which persistent foci of typhoid bacilli are primarily of import to the carriers themselves.

Localized Pyogenic Foci

The typhoid bacillus is not infrequently a pus producer, either alone or in combination with the staphylococcus or other microorganisms. Ulceration of the larynx is not uncommon during the disease, and parotitis is another complication that occurs. Otitis media is present in 2.5 per cent of all cases, according to Keen, and it may persist long after recovery. Bennett reports two cases, in one of which the typhoid bacillus was isolated from the pus of the middle ear four years after recovery from typhoid fever. One of the most frequent localizations of the typhoid bacillus, both during and after the disease, is in or about the bones. The organism is present in the bone marrow throughout the disease and characteristically localizes there in experimental animals. After recovery the bones may be affected in three general forms: periostitis, necrosis, and caries. Of these, periostitis is most usual and the tibia is the bone most frequently affected, after which follow ribs, sternum and the vertebrae. The bone infections may be multiple and persist for long periods of time. Fogh isolated the bacillus twenty-three years after recovery. Tubby, Braxton and Hicks found the bacillus in an abscess of the forearm thirteen years after an attack of enteric fever. Kaspar describes re-infection in the form of two successive bone abscesses, the last of which occurred seven and one-half years after recovery.

Gall Bladder Infection

In our discussion of the pathogenesis of typhoid fever we have already made reference to the uniformity and importance of localization of the typhoid bacillus in the gall bladder. As we have seen, the gall bladder serves as a reservoir and point for multiplication of the bacilli during the course of the active disease; it supplies the intestinal tract with increasing numbers of bacteria as the fever progresses; offers a potential source for reinfections and relapses; and, finally, may serve as a continued menace to others. The gall bladder in typhoid is therefore worthy of a more detailed consideration at this point.

Anton v. Fütterer (1888), was apparently the first to show that the typhoid bacillus could be isolated from the gall bladder in fatal cases of the disease. He obtained the microorganism in two such instances, commented on the lack of bactericidal property in the bile, and suggested that the presence of the bacillus in this locality might serve as a potential cause of relapse. V. Fütterer further showed that Bacillus pyocyaneus when injected into the circulation of rabbits could be found in the gall bladder in an hour and one-half. Similar experiments were later performed with the typhoid bacillus by Blackstein. In 1890, Gilbert and Girode found the typhoid bacillus in an acutely inflamed gall bladder removed during the course of the disease. It has since been shown repeatedly that the gall bladder contains the bacillus in the majority of cases of typhoid fever; Chiari [3] (1894) early obtained it in nineteen of twenty-two cases; Pratt somewhat later in twenty-one of thirty cases. It is obtained in nearly every case of the disease by modern methods. Scott actually found the organism in the gall bladder in twenty-four of twenty-eight positive typhoid cases, and also in six of two hundred cases without history of the disease, a matter of considerable interest in relation to the question of healthy carriers. Longcope [2] took bile cultures as a routine in suspected typhoid deaths when acting as pathologist to the Pennsylvania Hospital, and found the typhoid bacillus regularly in all positive cases. Human and bovine bile, at least, not only do not inhibit the growth of typhoid bacilli, but serve as a differential medium for its growth, as shown by Fraenkel and Kraus, a fact which has been made use of in Conradi's [3] differential medium for isolating the bacillus from the circulating blood, as we have seen. Stagnation of the bile apparently aids in the multiplication of the microorganism in the gall bladder (Pratt; Löwy), and it has been claimed by Posselt [2] that the

formation of albuminous flocculi which follows the growth of the bacillus, still further perfects it as a culture medium. There is histological and bacteriological evidence which shows that typhoid bacilli multiply not only in the bile but in the walls of the gall bladder itself, which leads us to a consideration of the exact method by which it actually reaches the gall bladder and the lesions it produces there.

The earlier observations by Gilbert and Girode, and Chiari [2, 3] in view of the then prevalent notion of typhoid as a purely intestinal disease, led them to assume that the bacillus reaches the gall bladder in an ascending route from the intestine. Birsch Hirschfeld was probably the first to state that the microorganism reaches the gall bladder through the circulation, a conception which has since then been experimentally verified and generally accepted. Experimental infection of the gall bladder in rabbits with a careful study of the artificial carrier condition in these animals has attracted considerable attention since the work of Fütterer, and particularly of Blachstein. Blachstein found that rabbits that have been given intravenous injections of cultures of the typhoid bacillus yield cultures from the gall bladder for days and weeks subsequently. The work of J. Koch, Chirolanza, Morgan, Johnston, Doerr, E. Blumenthal, Gay and Claypole, and others has shown not only that typhoid bacilli injected in this manner usually persist in the gall bladder for periods as long as nine months (Weinfurter) to be eliminated with the feces (Morgan), but, in short, produce a condition that is analogous to human chronic typhoid carriers. A certain percentage of rabbits die acutely after such an intravenous injection, but in the majority of instances perfectly normal animals survive the acute infection, the bacteria disappear from the blood in a few days, and finally become localized almost exclusively in the bone marrow and gall bladder, where they persist for weeks and months until the animal may eventually die of gradually increasing cachexia. This carrier condition may be produced with great regularity, in our experience, when cultures of the bacillus that have been grown on rabbit blood agar are employed for injection. Of forty-three normal rabbits that we utilized for this purpose, thirty-nine, or 90.6 per cent, became carriers. This experimental carrier condition offers obvious advantages for the study of the mechanism of gall bladder infection, of gall stone formation, and for testing various therapeutic agents designed to act on human carriers.

The rabbit experiments have shown, first, that bacteria injected intravenously arrive very rapidly in the gall bladder: E.

Blumenthal has shown, indeed, that they may be present there in ten minutes. Some difference of opinion has arisen as to the exact route traversed. Doerr, Lemierre and Abrami, and Nichols believe that the organisms pass from the portal circulation in the liver into the bile ducts. On the other hand, J. Koch and Chirolanza have shown not only that bacteria will reach the gall bladder promptly after ligation of the cystic duct, but have demonstrated nests of bacilli lying in relation to the capillaries of the gall bladder wall and apparently demonstrating ingress from this source. Personally we are inclined to believe that both routes are possible, as do Blumenthal and Baur, Jean, Hautefeuille and Sevestre. Passage through the liver seems a fairly certain and probably the usual route. Miss Lore Weber in our laboratory has been able to demonstrate typhoid bacilli histologically in transit from the blood spaces through the liver cell and into the bile capillaries. The matter is of more than academic interest in consideration of therapeutic measures.

Although the typhoid bacillus reaches the gall bladder in human cases of typhoid regularly and promptly after invasion of the circulation, its presence there is not as a rule evidenced symptomatically. Jaundice, cholecystitis, acute or purulent, and later gall stones do, however, not infrequently occur. The first two of these possibilities may afford the first and, indeed, the only symptoms of typhoid infection. Jaundice as a symptom apparently varies markedly in different groups or epidemics of typhoid fever cases. Posselt, in a systematic enumeration of such cases in various reported groups, found icterus present in from 0.14 per cent to 7.14 per cent of them. Sarrailhe and Clunet have recently described an epidemic of paratyphoid in the Dardanelles campaign that was characterized by jaundice and epigastric symptoms of cholecystitis. The "pyriform epigastric tumor" of the gall bladder (Frerichs) is given by Brouardel and Thoinot as one of the possible diagnostic signs of beginning typhoid. Gilbert and Girode, it will be recalled, first isolated the bacillus from the gall bladder of instances of acute cholecystitis in typhoid. Perforation of the gall bladder and localized peritonitis is one of the rarer accidents that may happen. In the majority of cases no definitely localizing symptoms, except possibly pain on epigastric pressure, give evidence of the inevitable localization of the bacilli in the gall bladder. It seems probable, however, that minor histological changes occur in all cases. Hölscher has noted the presence of a diphtheritic inflammation of the gall bladder in 0.25 per cent of two thousand typhoid autopsies. In artificially infected rabbits

changes in the gall bladder are usually evident within a few days; the viscus gradually becomes distended even to two or three times its natural size. The bile, which at first may be thicker and darker than normal, assumes a milky appearance, owing to accumulation of small white flocculi which on standing separate out, leaving a clear, nearly colorless fluid. A similar description of the gall bladder contents has been given in the case of acute cholecystitis in a proved typhoid carrier by Findlay and Buchanan. In rabbits, erosions of the mucosa appear and proceed until the muscularis coat is laid bare. In more advanced stages the gall bladder walls become thickened and the bile more nearly normal in appearance. Apparently identical conditions have also been found in chronic human carriers by Bindseil, by Messerschmidt and by Goebel.

One of the most important sequels of the invasion of the gall bladder by typhoid bacilli is the production of gall stones. Naunyn noted as early as 1892 that a relatively large number of his gall stone cases gave a history of previous typhoid fever. Cushing found such a previous history in ten of thirty-one cases in the Johns Hopkins Hospital. Forster obtained a history of gall stone attacks in fourteen per cent of 173 chronic intestinal typhoid carriers. Klinger's [2] figures (1909) show 13.6 per cent of carriers with gall stone symptoms. These figures, as showing a causative relation, are surprisingly high when we consider that ninety per cent of individuals with gall stones never suffer from actual symptoms. The instances of gall stones without history of previous typhoid are explicable, first, by the fact that other bacteria, as for example Bacillus coli and streptococci, undoubtedly produce them, and, secondly, we have in the case of healthy carriers undoubted evidence of the invasion of the gall bladder by typhoid bacilli in the usual manner, without symptomatic typhoid fever. In Cushing's cases the typhoid bacillus was isolated from gall stones in an individual who gave no previous history of typhoid, and F. Blumenthal has reported two similar cases.

Typhoid bacilli have frequently been obtained in pure culture from gall stones. Droba early found them as long as seventeen years after recovery from the disease itself. It is evident that these stones occurring in connection with typhoid bacilli may be rapidly formed; in Pratt's third reported case they were present in stones removed on the eighteenth day of the fever. Milian obtained similar results on the sixteenth day. The actual mode of formation of these gall stones is of interest but by no means clearly understood. There is evidence that typhoid bacilli may pene-

trate gall stones that are already formed. On the other hand, Kramer and Bachmeister have demonstrated that cultures not only of Bacillus typhosus, but of Bacillus coli and Bacillus pyocyaneus, when grown in sterile bile will cause crystals of cholesterin to separate out and to form small concretions. Richardson early showed that the typhoid bacilli which he found in the gall bladder were characteristically clumped, although more recent work by Venema and others would indicate that bile has in itself no real agglutinating action.

Gilbert and Fournier proved the infectious origin of at least certain gall stones by injecting heated bouillon cultures of typhoid bacilli into the gall bladder of rabbits; they found small concretions in the bladder when such animals were subsequently sacrificed. Richardson [2] found gall stones in certain of his carrier rabbits. We have observed these formations in our rabbits, varying in all degrees from pin-head, friable concretions to hard, facetted stones as large as a cubic centimeter in diameter, packed in and completely filling a distended gall bladder.

It is evident that the condition in experimental rabbits presents a close analogy to the residual aspects of human typhoid infection, except that persistence of the bacteria in the gall bladder of these animals is the rule rather than the exception. Normal rabbit bile, however, according to Nichols, is a less favorable medium for the growth of the typhoid bacillus than human bile. The typhoid bacilli soon disappear from the peripheral circulation in rabbits and coincidently agglutinins and fixation antibodies (Aoki) appear. The analogy is further strengthened by the fact that the appearance of the bacteria in the excreta in carrier rabbits is intermittent (Emmerich and Wagner) as in chronic human carriers. When rabbits have first been immunized by subcutaneous or intravenous injections of typhoid vaccines, they do not become carriers on intravenous injection of a dose of living microorganisms, that produces the condition in normal animals (Gay and Claypole [3]). They may, however, still be locally infected by injections directly into the gall bladder (Uhlenhuth and Messerschmidt; Emmerich and Wagner), or even by intravenous doses when sufficient to overcome the increased bactericidal effect of the blood (Nichols). This latter condition again suggests chronic human carriers who are usually protected from generalized typhoid infection, although it is known that auto-reinfection may exceptionally occur.

THE CARRIER STATE

Our consideration of the residual foci of typhoid bacilli in the human body has been not only to point out their intrinsic importance, but to serve as introductory to a description of the carrier condition. The persistence of typhoid bacilli in the body after recovery from typhoid fever indeed affects the individual less than it does the community. Incidental reference has been made in discussing the transmissibility of typhoid fever to the earlier observations of Gendron, of Budd [2] and of Klebs,[3] which indicated that fresh cases of the disease might be traced not only to typhoid patients, but to convalescents. The actual major sources of infection from convalescents in feces and urine were further indicated by Budd [1, 2, 3] (1856) and by Petruschy (1898). We owe our true epidemiological conception of the importance of the typhoid carrier state primarily to Robert Koch, as stated in his address of November, 1902. Koch [2] there emphasized the importance of the typhoid patient and the typhoid convalescent as the primary source of further infection and recommended the establishment of experimental stations in certain parts of Germany in which typhoid fever was very prevalent. The first of these stations was established at Treves in 1903 under the direction of Frosch, and by the year 1907 eleven such laboratories were running. To Drigalski is due the larger part of the credit of establishing on bacteriological grounds the concrete hypothesis suggested by Frosch that the typhoid bacillus may lead a saprophytic existence in the intestine long after recovery and be the cause of new cases, and further in collaboration with Conradi the credit of proving the existence of healthy carriers. These and other investigations conducted in the German laboratories give us much of the information we now possess in reference to typhoid carriers, and this information, together with the introduction of typhoid vaccination, is responsible for the remarkable reduction of the disease in recent years. The data on this important subject are so recent and so extensive that they cannot as yet be grasped in their full significance. We attach particular value to the efforts of Sacquépée, and of Ledingham and Arkwright to present comprehensive reviews of the typhoid carrier problem, and have made use freely of their authoritative monographs in preparing this chapter.

Classification of Typhoid Carriers

Typhoid carriers may first of all be classified in respect to the mode of elimination of the bacteria. These modes of elimination are obviously dependent on the residual foci of typhoid bacilli, of which the most important is the gall bladder with elimination through the feces, and, secondly, the urinary tract with discharge through the urine. And, lastly, any of the localized purulent foci of typhoid bacilli, as otitis media or periostitis, may potentially, although rarely in practice, serve as sources of further infection. Our subsequent remarks deal largely with intestinal carriers, and for that reason we may at this point mention certain important facts concerning urinary carriers.

Urinary Carriers.—Urinary carriers are much less common than intestinal carriers, although they may be individually more dangerous owing to the more indiscriminate distribution of urine and the relatively larger numbers that are discharged by this route. In certain instances the turbid urine may contain as many as a hundred million bacteria to the cubic centimeter. In the chapter on diagnosis we have already considered certain relations of the typhoid bacillus to the urinary tract. Konjajeff early (1899) found small metastatic nests of bacteria in stained sections of the kidneys in certain typhoid cases, and Hueppe had isolated the organism from the urine in 1886. We know that by the second or third week of the active disease the bacillus can be found in from twenty-five to fifty per cent of cases in the urine, although it does not persist there as frequently as in the stools. Petruschy in 1898, pointed out the danger of spread of the disease from the urine of convalescent cases, and in the same year Rovsing reported a case of cystitis that had recovered from typhoid eighteen months previously, and found large numbers of bacilli in a badly ulcerated bladder on operation. At autopsy a month later numerous small abscesses were found in both kidneys. In some instances urinary carriers have been found who give no history of typhoid fever, a condition by no means uncommon, as we shall see in intestinal carriers. Bacteria may be discharged for a limited period of time both in urine and feces, but the persistent carriers in the urine are usually restricted to this mode of dissemination. The principal source of the bacteria in urinary carriers is the pelvis of the kidney rather than the bladder, although a secondary focus may also be present in the latter organ. A chronic carrier condition is by no means dependent on profound structural changes in the kidney

or the bladder, as in the case we have referred to. It is by no means certain that urinary carriers bear any relation to the cases of so-called nephro-typhoid or of cases of typhoid cystitis. As indicative of the proportion of urinary to intestinal carriers, Prigge [2] found that of 314 carriers only twenty-three, or seven per cent, were pure urinary carriers; and of these, sixteen were healthy carriers who had acquired the bacteria by association with typhoid cases. The duration of urinary carriers is probably not as long on the average as of intestinal carriers, owing to the fact that the condition is more accessible to local treatment. Prigge mentions a case of nine years' duration, and one of ten years has been reported by Meyer and Ahreiner.

Typhoid carriers, again, may be classified in their relation to an actual attack of typhoid fever. Several such classifications have been made, notably by Conradi (1907), by Prigge (1909), and by Sacquépée (1910). The latter is by far the most comprehensive and satisfactory. According to Sacquépée, carriers are comprised of the following groups and subgroups:

Group I. Precocious or incubation carriers. These consist of those individuals who have ingested typhoid bacilli and are beginning to eliminate them without having as yet shown symptoms of typhoid fever.

Group II. Carriers that have recovered from typhoid fever, who may be subdivided in respect to duration into:

A. Convalescent carriers. Individuals who eliminate bacteria up to three months after recovery.

B. Chronic carriers. Individuals who eliminate from three months after recovery to indefinite periods of time.

Group III. Healthy or paradoxical carriers—with no history of typhoid fever.

We may proceed to an examination of the important facts characteristic of each of these groups of carriers.

Carriers in Recovered Typhoid Cases.—Recovered cases of typhoid fever presented the logical material for the earlier investigations of the carrier state. The elimination of typhoid bacilli for a period, which for convenience has been placed at three months, after recovery constitutes temporary or convalescent carriers. Such individuals were described first by Decobert, who found bacteria in the stools of twelve cases for from fifteen to twenty days after recovery from typhoid fever.

Drigalski in 1904 reported on sixty-four cases both during and subsequent to recovery from the disease, and showed that bacteria might also persist for months in the stools.

We owe the complete demonstration of chronic or continued carriers largely to the thoroughness of German investigations. Continued examinations of the excreta of convalescent cases soon showed that excretion of typhoid bacilli may continue not only for a few weeks but for months and years. The direct evidence afforded by following authenticated cases for several years has since been supplemented by the demonstration of typhoid bacilli in the excreta of individuals who give straightforward though naturally less conclusive histories of typhoid fever, even as long as forty or fifty years previously (Bolduan and Noble, 46 years; Gregg, 52 years). Such evidence shows that the carrier condition may persist for indefinite periods after recovery. It is apparent, then, not only that such a chronic carrier continues individually to be a menace, but that collectively their number is cumulative. It is, therefore, of importance to know in what percentage of recovered cases chronic carriers may be expected. As illustrative of efforts that have been made to determine this important point, we offer herewith a table summarizing results from the study of over 1,900 convalescent cases reported between the years 1905 and 1910 (Table XI).

TABLE XI

PERCENTAGES OF CHRONIC TYPHOID CARRIERS FOUND BY VARIOUS INVESTIGATORS IN A STUDY OF CONVALESCENT CASES

Author	*Date*	*No. of Cases*	*Percentage Carriers for 3 mos. and more*
Lentz	1905	400	3
Conradi [2]	1907	400	0.5
Klinger	1907	482	1.7
Kayser	1907	101	3–5
Semple & Greig	1908	86	11.6
Park [2]	1908	68	5.9
Tsuzuki	1910	51	5.8
Bruckner [2]	1910	316	3.8
Stokes & Clarke	1916	810	1.85

It is evident from this table that continued excretion of the typhoid bacillus, largely through the feces, may be anticipated in four or five per cent of all recovered cases. There is no reason to assume that once the chronic carrier state has been established, at a period arbitrarily placed at three months after recovery, the excretion of bacteria becomes progressively less with succeeding months and years; in fact, all evidence points to the contrary. These percentages are certainly under the true percentages, owing

not only to the difficulty in isolating typhoid bacilli from the feces of relatively normal individuals even when cathartics are employed, but to the fact that the discharge of the microorganisms in carriers is characteristically intermittent. Thus, the high percentage of 11.6 per cent reported from the Central Research Institute at Kasauli in India by Semple and Greig more nearly represents the true state of affairs, as the search for bacilli was made daily until the stools were repeatedly negative. But, if we assume as a minimum that five per cent of all recovered cases become chronic carriers and we know that over 150,000 recovered typhoid cases are still being produced each year in the United States, we have some 7,500 carriers added annually to a presumably cumulative list. It is evident how important any measures directed towards the detection and cure of these fundamental sources of further typhoid infection become.

Precocious or Incubation-Period Carriers.—It has been clearly shown by a number of authors, notably by Mayer, by Simon and by Conradi, that certain individuals may excrete typhoid bacilli in their feces before they themselves actually come down with symptoms of typhoid fever. These individuals are particularly dangerous sources of infection because they are unsuspected. The exact mechanism by which this excretion takes place before the symptoms is not clearly understood. We have already seen that typhoid bacilli do not appear in considerable numbers in the feces until a generalized bacteremia has taken place and invasion of the gall bladder has occurred. In the majority of such instances, when such a distribution of the bacillus has taken place in the body, symptoms of the disease are already evident. On the other hand, we shall presently see that in the so-called healthy carriers a generalized invasion by the typhoid bacillus must have occurred with a subsequent permanent localization in the gall bladder, although no symptoms ever occur. It seems necessary to assume in the case of incubation carriers that the evolution of the disease symptoms has simply been delayed beyond the usual period following general invasion of the typhoid bacillus. In the majority of instances these incubation carriers have been detected for relatively short periods before the appearance of symptoms, usually from two or three days to a week or so. Certain observations of Battlehner make it more than likely that incubation carriers, as we have suggested, simply represent a transition condition between healthy carriers and the normal evolution of typhoid fever. Battlehner has reported seven incubation carrier cases, in four of which typhoid bacilli were detected in the excreta for from twenty-

one to 117 days before the appearance of fever. The one case that was prolonged for 117 days is of particular interest in this connection; this individual, it would seem, may properly be regarded as a healthy carrier who finally succumbed to autoinfection. The agglutination reaction in the serum of this particular case was at first positive in a dilution of one to fifty, thus indicating a resistance to infection, but shortly before fever appeared it became negative.

Healthy Carriers.—A thorough bacteriological survey of excreta in a general population irrespective of any previous relation to typhoid fever will show, as may be imagined from the fact that some of them have suffered from typhoid fever, a definite number of typhoid carriers. Four such determinations that have been made are included in the following table.

TABLE XII

OCCURRENCE OF TYPHOID CARRIERS IN THE GENERAL POPULATION

Author	*Date*	*Locality*	*Cases Examined*	*Percentage of Carriers*
Minelli	1906	Prison, Strassburg	250	0.4
Rosenau, Lumsden & Kastle	1909	Washington	993	0.3
Prigge	1909	Saărbrucken	10,841	0.29
Muller, P. T.	1916	Germany	20,019	0.8
				Including typhoid, paratyphoid and dysentery

There is a singularly close agreement in these figures as to general occurrence of carriers, and an estimate of three carriers in every 1000 people must be regarded as extremely conservative when we consider the intermittence of the carrier state, the unfavorableness of normal stools for such examinations, and the difficulties in detecting the bacillus under the most favorable conditions.

Our interest at this point attaches to the fact that if in investigations of this sort careful inquiry as to the history of previous typhoid fever in positive carrier cases is made, it will be found that a certain number of individuals give no history of the disease. In a number of the earlier investigations on the distribution of typhoid bacilli, as for example those that were reported by Remlinger and Schneider in 1896, it was claimed that these organisms were found in the stools of perfectly healthy individuals. Owing to cultural difficulties, the typhoid bacillus was not clearly differentiated from

the colon bacillus at this time, and it appears certain that it remained for Drigalski and Conradi to demonstrate that healthy carriers of the typhoid bacillus really existed. Their observations in 1902 were corroborated two years later by Cler and Ferazzi, who found six positive transitory carriers among thirty-nine normal individuals who had partaken of infected food that gave typhoid fever to others in the group. The actual percentage of these healthy carriers that may occur in a community was concretely expressed in the statistics compiled by Klinger [2] from a study of 431 carriers detected in a population of 2,300,000 in South West Germany. Of these 431 carriers, 220 were chronic by the three months standard we have already given, and forty-four of the latter (20 per cent) gave no history of typhoid fever. Among the transitory carriers there were actually more healthy than recovered carriers, 119 to 92 in fact. The total figures show that thirty-seven per cent of all the carriers found gave no previous history of the disease.

These surprising figures probably exaggerate to some extent the proportion of healthy carriers that would be found in a general population. The material from which they have been drawn has been obtained from localities in which typhoid is rampant, and there are other figures which show that healthy carriers are particularly prevalent in such districts. Klinger has shown that over 0.6 per cent of 1700 healthy individuals in the vicinity of typhoid cases were carriers. Dennemark found four healthy individuals out of 250 (1.6 per cent), who had been exposed to cases of typhoid fever, who gave positive Widals and had typhoid bacilli in their stools. Scheller found eighteen healthy carriers among forty-four individuals who had used milk contaminated with typhoid bacilli; thirty-two others of the same group actually acquired the disease.

As may be judged from the later statistics of Klinger, to which we have referred, the percentage of temporary carriers among healthy disseminators of typhoid bacilli is particularly high. Fornet, however, found that seventy-eight of 187 healthy carriers, whom he studied between 1904 and 1909, continued to excrete typhoid bacilli for months and years. The designation healthy carriers comprises, in addition to those who have actually suffered no symptoms of typhoid fever whatsoever, in other words, the true healthy carriers, many mild and unrecognized instances of the disease. These mild cases are particularly prevalent among children and are also characteristic in certain epidemics such as the one described in the French garrison by Billet, Le Bilian, Therault, Lamande, Lutrot and Louis, who describes all gradations of cases,

some with constipation only, with fever lasting only two days, or even cases with complete apyrexia, and yet many of them giving positive cultures in the stools. Such cases in the absence of an epidemic would never be recognized as true typhoid, and yet would serve as potential sources for new infections.

It should be repeated that the course of the typhoid bacillus through the body of the healthy carrier and its final localization in the gall bladder is precisely the same as in the recovered cases of typhoid fever. This fact has been conclusively proved by the finding of typhoid bacilli in the blood of healthy individuals (Conradi,[2] Busse, Mayer, and Ebeling); and by the detection of the bacilli in gall bladder and gall stones of those with no previous history of the disease. For example, Scott could cultivate the typhoid bacillus from the gall bladder at autopsy in six out of 200 individuals who gave absolutely no history of typhoid fever. Blassberg has not infrequently found typhoid bacilli in terminal cases of tuberculosis that gave no indications of typhoid fever.

Importance of Carriers as a Source of Typhoid Fever

In our consideration of the modes of transmission of typhoid fever we have found that they may in general be divided into contact and water infections. Contact infections are direct or indirect, and the latter may form a chain of several and of different links. And, again, water containing Bacillus typhosus may reach the mouth directly or indirectly. In all instances the typhoid bacilli originate in excreta, particularly in the feces, either from an individual ill of typhoid or from a typhoid carrier. Any of the routes of typhoid infection outlined may be traced to a typhoid carrier as well as to a typhoid patient, but certain routes are more characteristically associated with each of these conditions. Typhoid fever is transmitted from patients more particularly by direct contact or by water, from carriers preëminently by indirect contact. Carriers transmit typhoid to others most frequently of all by the contamination of food.

Carriers give rise either to individual cases or to epidemics, according to the intimacy of their relations with others and their occupation. They are particularly dangerous because they continue a source of infection for indefinite periods of time and because they are usually unsuspected. We have seen that there is an increasing agreement as to the relative percentage of typhoid cases attributable to each of the three great channels of infection, contact, water, and milk. We have less information and therefore less agreement concerning the importance of typhoid

patients and of typhoid carriers as the source of infection. This is due partly to the relatively recent demonstration of the carrier state on bacteriological grounds, and to some extent to the failure of epidemiologists to trace epidemics, to say nothing of individual cases, back to the previous individual from which the infecting dose was derived. That many cases of typhoid fever are due to carriers is undoubted, but exactly what percentage of them at any time or place is uncertain. In the following table we have grouped the estimates of a number of German investigators from material for the most part already presented in other connections.

TABLE XIII

ESTIMATED PERCENTAGE OF CASES OF TYPHOID FEVER IN GIVEN GROUPS ORIGINATING FROM TYPHOID CARRIERS

Author	*Date*	*Locality*	*No. of Cases*	*Percentage Due to Carriers*
Frosch	1907	Strassburg	6708	4.11
Forster	1908	"	386	20.0
Kayser	1909	"	505	9.5
Schumacher	1909	Crov	45	26.6
G. Mayer	1910	Bavarian Palatinate	495	32.3

It will be seen that the tendency of these percentages of cases attributable to carriers rises with the later years. This is due in part to better criteria of estimation and greater success in tracing each case to its source. Thus, in Kayser's summary 26.7 per cent of cases were attributed to milk infection and at least part, probably the majority of these, were originally due to carriers. In the figures both of Mayer and of Schumacher the epidemiological work was very thorough. On most conservative grounds it would seem safe to attribute twenty-five to thirty per cent of all cases of typhoid to carriers. If all chains of cases are traced to the original link, it is probable that in even a higher percentage of cases carriers will be found at the beginning. Brückner has reported on typhoid outbreaks that occurred in Saärbrucken in 1911. There were twenty-eight such epidemic chains consisting each of from six to sixty-nine cases. Precisely one-half of these chains, fourteen in number, began with a carrier who in most instances communicated infection through food stuffs. Garbat [2] has recently estimated that fifty-five per cent of all typhoid cases may be traced directly or indirectly to carriers.

General Facts in Reference to Carriers

There are certain facts of interest in connection with the carrier state in its relation to age and sex. There is an enormous preponderance of females over males among the chronic carriers, something like five to one. The number of transitory carriers is practically the same in the two sexes. No direct explanation of the cause of this difference in the number of chronic carriers between the two sexes is available, although several suggestions have been made that are at least probable. These differences, again, are in a similar proportion to the occurrence of gall stones, and both conditions may predominate in women, owing to feminine characteristics which tend to interfere with the portal circulation, namely, lacing, pregnancy and menstruation.

Chronic carriers occur maximally at between forty and forty-five years of age and are rare in children, although the latter afford the highest percentage of transitory carriers.

The actual danger of a given carrier is to a great extent dependent on the occupation which he or she follows. Food contamination accounts for the majority of cases that are derived from carriers, and those who have to do with the preparation or handling of food are the most prolific disseminators of the disease. Cooks, marketmen, who handle food stuffs, and milkmen have been the most frequent originators of carrier epidemics. The number and the distribution of cases will depend on the relation of the food preparer or handler to the general public. Cases due in this manner to food contamination are grouped characteristically in houses or institutions served by a carrier cook, or along milk routes followed by a carrier milkman. Any grouping of people in close proximity also tends to enhance the infecting possibilities of a carrier, apart from food contamination. Armies, prisons, and insane hospitals are particularly liable to epidemics originated in this manner. In a number of instances epidemics and scattered cases have been traced to carriers on shipboard (Sawyer [3]).

We have already referred to the intermittence in elimination of typhoid bacilli by chronic carriers. These differences would apparently lie beyond mere technical difficulties in detecting the typhoid bacillus, and seem at present inexplicable. This intermittence is evident not only from positive and negative bacteriological findings, but from variation in the number of bacteria excreted at different times.

Efforts have been made to show differences in the virulence of

bacteria obtained from different carriers, or, again, from carriers in contradistinction to typhoid cases. The only criteria of estimation of such differences is the relative pathogenicity of different strains of bacteria for experimental animals. This method, we believe, is of no value in relation to human infection, and, although there may be certain immunological differences between typhoid bacilli derived from blood or stool cultures, there would seem no method of proving experimentally that one strain is less liable to infect than another, or that another gives rise to a more severe form of the disease.

Conversely, there are certain indications that suggest that newcomers when exposed to typhoid carriers are more susceptible to infection than those who have long dwelt in their vicinity. These indications, although interesting, are not supported by rigorous statistical or experimental proof and are subject to the same skeptical acceptance as are those instances of natural immunity which we shall later consider.

Typhoid carriers are for the most part personally unaffected by their condition, which is such a menace to others. They may, however, as we have seen, suffer from cholecystitis, from gall stones or from inflammation of the urinary bladder. In addition, there is the possibility of auto-reinfection, as has been shown by Levy and Kayser,[2] and by Grimme. The two fundamental and as yet unanswered questions underlying the carrier state are, first, why the typhoid bacillus which promptly localizes in the gall bladder in all typhoid cases remains there in only four or five per cent of them; and, secondly, why, having persisted in the gall bladder, it fails to produce typhoid fever in the host at some subsequent period. The second question is obviously bound up in the explanation of acquired typhoid immunity. We shall later see that the protection against typhoid fever, which is relatively great and constant after recovery from the disease, is probably a tissue immunity; in the typhoid carrier it appears that a localized (lymphatic) tissue immunity may co-exist with a localized (gall bladder) tissue hypersusceptibility.

The Detection of Carriers

One of the greatest advances that could be made in the suppression of typhoid fever would be a rapid method for detecting carriers. In non-carrier typhoid recoveries, positive serum reactions are exceptional for any considerable period of time after recovery. Agglutinins, opsonins and fixation antibodies, on the other hand, are frequently but by no means invariably present

in carriers. The agglutination reaction is positive in from two-thirds to three-quarters of those in whom typhoid bacilli persist, and more frequently in recovered than in healthy carriers. Another possible diagnostic test for carriers might lie in the demonstration of a leucopenia, which, as Leydhecker has shown, occurs not infrequently.

The only certain and always necessary method in detecting carriers lies in an actual demonstration of the typhoid bacillus in their excreta. We have fully considered the methods for isolation of the typhoid bacillus from the stools and urine, many of which have been developed more particularly in connection with a study of the carrier state, and we need not consider them here in more detail. The laboriousness of these methods when applied to large groups of individuals, as is usually necessary in detecting a carrier, is apparent.

CHAPTER VIII

GENERAL MEASURES OF PREVENTION OF TYPHOID FEVER

We have finished our survey of the life history of typhoid infection. We have considered the animate agent, the typhoid bacillus, which is the single essential cause of the disease, and have examined in turn its methods of entering the human body, its development therein, and, finally, its methods and times of exit. From the latter point it is ready to begin again its characteristic and dangerous life cycle in another human being. It is obvious from all that we have seen that the typhoid bacillus is the only essential factor in the propagation of typhoid fever, although its task may be facilitated by a number of secondary factors extrinsic and intrinsic to the life of its host. The prevention of typhoid fever lies therefore either in the destruction of the typhoid bacillus, or in preventing it from approaching human beings.

From what we know of the modes of typhoid infection it is apparent that the typhoid bacillus may be dealt with at three points: on its egress from the typhoid patient or carrier; in transit from one individual to another; and, again, at the portals of entry of its prospective victim. Let us consider in this and the following chapters the methods of preventing the disease in accordance with these three loci of attack on the typhoid bacillus.

THE PREVENTION OF TYPHOID FEVER AT ITS SOURCE

Typhoid infection in common with other evils is best prevented at its source. It is perfectly true that typhoid bacilli from the moment they leave the ideal conditions for development furnished by the human body, tend rapidly to diminish in number, with few if any exceptions. This diminution in numbers is, however, from the viewpoint of prophylaxis more than offset by the greater dissemination of the bacteria and thereby the more numerous and less evident contaminated sources which are produced. Although only a few of the original microorganisms may survive in any given locality, they may still be sufficient to produce infection. The prevention of typhoid at its source resolves itself into the proper

methods of dealing with excreta, and these methods will differ essentially in accordance with whether the particular source under consideration is a typhoid patient or a typhoid carrier, and so each of these individuals must be considered separately.

Prevention of the Extension of Typhoid Fever from Typhoid Patients

The extension of typhoid fever from known typhoid patients can and should be absolutely prevented. The full observance of even the simple rules laid down by Budd would suffice not only to prevent epidemics, as he did, but even single cases among those who surround the patient. The difficulty no longer lies so much in preventing new infections from known typhoid fever patients as from those in the incubation period of the disease, or those in whom diagnosis is not yet certain. There would seem no way of avoiding possible infection from apparently healthy incubation carriers, except in the observance of general rules of hygiene, such as washing the hands before meals and after defecation and micturition, which, although frequently preached and rather generally appreciated, are rarely rigorously practiced. If every individual were to treat himself as a possible carrier in so far as personal cleanliness is concerned, this particular source of danger would be obviated, not only for typhoid fever, but for a number of other diseases as well.

The earlier days of typhoid fever are scarcely less dangerous from the point of further infection than the incubation period. Once the patient takes to his bed the danger must to some extent be diminished, even in the absence of diagnosis, for the area of contact with others is diminished and his hygiene passes under the supervision of others. The best method of general prophylaxis lies in the partial isolation of any febrile patient, rigorous sterilization, or at least proper disposal of the excreta, and, as rapidly as possible, an assured diagnosis. The most certain method of obtaining this diagnosis in earlier stages of the disease lies, as we have seen, in a blood culture, which should certainly be taken in all suspected febrile cases, and should be rendered more generally available for the general practitioner. The work of Conradi and of Klinger,[2] as tabulated by Ledingham and Arkwright, shows clearly that the danger from unsuspected and undiagnosed early cases is a real one. Their statistics show that the greater number of secondary cases of typhoid are derived from primary cases in the incubation period and two earlier weeks of the disease, as illustrated in the following figures (Table XIV).

TABLE XIV

STATISTICS OF TIME OF INFECTION OF CONTACT CASES FROM PRIMARY CASES (KLINGER [2])

Incubation Period	*No. of Cases*
First week	33
Second week	150
Course of the Disease	
First week	187
Second week	158
Third week	116
Fourth week	59
Fifth week	34

The figures show the greater danger of early cases in which diagnosis is unsuspected or doubtful, and are the more striking when we consider that actually more bacteria are eliminated from the third week of the disease onward, both in feces and urine.

The menace of typhoid fever patients is not only direct in that they may give rise to the disease in others, but indirect in that they may produce healthy carriers, who have been shown to be more numerous in the neighborhood of typhoid cases than elsewhere in the community, and who in turn may transmit infection.

Once typhoid fever is recognized, prevention of the extension of the disease from that particular source may be and should be absolute. Such prevention depends on the following out of certain definite rules, applicable both to the patient and to those who attend him. First and foremost, typhoid fever is in most communities, and should be in all, a reportable disease, the reporting serving to signalize the presence of a definite but avoidable danger to those who come into the vicinity of the patient. The clinical history of the case should comprise as full an account as possible, not only of the actual duration of the disease before its recognition, but of any possible source of contagion to which infection may be traced. The history of excursions into the country, of drinking from suspicious water sources, of bathing in polluted streams in the neighborhood of recognized or unrecognized febrile cases, and the like, should be inquired after. The milk supply used by the patient in question should be ascertained in order that other cases that may occur on the same milk route may be correlated, and, when present, aid in tracing the individual, probably a carrier, who has contaminated the milk.

As has already been stated, the patient should be isolated, preferably in a hospital, or if in a private house, at least in a room

separate from other members of the family. The floors of the room should be cleaned by means of damp cloths wet with phenol solution or bichloride of mercury, and every effort made to prevent raising a dust. No particular precautions are necessary in attempting disinfection of the air or in cleansing the walls. The windows of the room should be screened in order to prevent the access of flies to the patient's excreta. Every article or utensil that comes in contact with the patient should first of all be set apart for his particular use, and should be carefully disinfected before leaving the sick room. Bed linen and body clothes may be soaked in an antiseptic solution of bichloride or of phenol, and then preferably boiled. Eating utensils should be boiled before they are used again. If proper precautions are taken during the course of the disease, no terminal sterilization of the room is regarded as necessary by modern public health authorities.

The greatest possible care should be taken in the disposal of the excreta, particularly of the feces and the urine, from the typhoid fever patient. Sputum may either be expectorated directly into a glass or porcelain receptable containing five per cent carbolic acid or bichloride solution 1–1000, or collected on cloths and burned. The urine and feces are collected in a suitable bedpan, which should be separately sterilized after using by lysol, carbolic acid, or bichloride. The buttocks should be washed in a dilute solution, say one to 4000, of bichloride after defecation. Thermometers, particularly when used for taking rectal temperatures, should be kept in dilute phenol solution and rinsed in running water before being employed again. The feces after collection should be allowed to stand in a suitable disinfecting solution in proper amount and for a sufficient space of time. If the feces are not fluid, the masses should be broken by stirring, in order that the solution may penetrate thoroughly. A number of different disinfectants have been suggested for the purpose of disinfecting, among which may be mentioned bichloride of mercury in a dilution of one to 1000, added in proportion of from one-fortieth to one-tenth of the volume of material to be disinfected; formalin ten per cent in the proportion of one to ten; carbolic acid five per cent in the proportion of three or four to ten. For most purposes, on account of its relative cheapness and quicker action, the bichloride solution is usually preferable. Calcium hydroxide (milk of lime) may be added in proportion of one to eight. Both copper sulphate, as recommended by Vincent, or ferrous sulphate, as originally recommended by Budd, are also suitable disinfectants. Bleaching powder in a three per cent solution is also efficacious. The urine may be sterilized

by the addition of bichloride, of formalin, or of carbolic acid, and the elimination of bacteria by this route is certainly to some extent inhibited by the administration of urotropin, the value of which will be more fully considered in connection with carriers. In general, contact with the disinfecting solutions should be for an hour or more.

The bath water should be sterilized after using, the addition of one-half a pound of chloride of lime being sufficient to disinfect two hundred liters in thirty minutes.

In addition, it may be pointed out that the dead bodies of typhoid fever patients offer certain dangers of infection. This is notably true in the performance of autopsies, where the greatest precaution should be taken by those engaged in their conduct. The external orifices of the nose, mouth and anus should be stuffed with cotton impregnated with a strong solution of bichloride or of phenol.

A separate set of precautions should be taken by nurses or other attendants on typhoid cases. First of all, they should be fully protected by recent vaccination against typhoid fever, as will be fully specified in later chapters. Rigorous care should be taken to disinfect the hands by soap and water or by a mixture of denatured fifty per cent alcohol and liquid soap, as suggested by Joetten. When engaged in the intimate toilet of typhoid cases it is advantageous at times to wear rubber gloves, which are placed in a disinfecting solution when not in use, and rubber aprons may be utilized to advantage, particularly when bathing the patient. Great care should be taken by nurses to avoid, if possible, the preparation of food for others and even for themselves, but when this becomes necessary, additional precautions in sterilizing the hands should be taken before handling any food stuffs.

Prevention of Extension from Typhoid Carriers

Any typhoid carrier is a potential source of typhoid fever, and the considerable proportion of all cases which are due to them has already been sufficiently emphasized. The dangers are great enough when carriers are recognized as such, but still greater during that often prolonged period during which they escape recognition. Short of comprehensive bacteriological examinations of whole communities, it will probably never be possible to recognize all of these unsuspected carriers. Certain precautions may be suggested, however, which will minimize the danger from this source. Carriers usually become recognized by careful

epidemiological surveys in connection with repeated cases of typhoid fever in a given locality, in association with some particular individual over a period of time, or in connection with some epidemic due to food, in the preparation of which he, or more frequently she, has taken part. In such surveys it is usually possible by a process of elimination to identify the carrier or carriers in a given group of individuals. The method by which this elimination is carried on will depend to a large extent on the individual skill, tact and experience of the epidemiologist. In dealing with people of various temperaments, who must be rigorously questioned as to present and past history, tact frequently is as important as knowledge. The past history of a prolonged fever, which may or may not have been designated as typhoid, is the first point of inquiry. Healthy carriers may frequently be detected by questions in relation to gall stone attacks or even to icterus.

Final identification must rest in all instances on the demonstration of typhoid bacilli in the excreta, and it may be necessary to examine many individuals and perhaps each several times to reach a final conclusion.

Under ideal conditions of public health administration every recovered typhoid carrier at least would be known to the authorities and his relations to others properly controlled. Theoretically no convalescent typhoid patient should be discharged without knowledge as to whether he is or is not a carrier of typhoid bacilli. In case he continues to excrete bacteria his liberation may at least be delayed, and before he returns to his usual life he should have been taught to appreciate his potential danger to the community. No convalescent may be discharged as normal until four negative bacteriological examinations of his stools and urine have been obtained. Flatten has suggested that the period of four weeks after the return to normal temperature, which is advisable for the welfare of the patient himself, gives ample time for sufficient examinations of the stools, which in at least ninety per cent of cases become normal during this period. As a matter of fact, however, the excreta of convalescents are seldom examined. This is true not only of cases in private practices but also, unfortunately, in most of even the best hospitals. Garbat [2] reports that according to answers to a questionnaire sent out by Dr. F. S. Graves only nine of twenty-four leading hospitals in this country examine the excreta of their typhoid patients before discharge.

The early detection of carriers is very important in armies,

not only in the body of troops itself, but in the inhabitants of captured towns, where typhoid has been prevalent. Systematic investigations of this sort have actually been carried out by German army physicians, according to Uhlenhuth. It is further highly desirable to detect carriers among cooks and others engaged in the preparation of food. In New York City a food handler's card is issued by the Board of Health, which is necessary in order to secure a position of this nature. In the absence of a bacteriological examination of this sort a history of previous typhoid fever might be taken into consideration in choosing among individual applicants for positions of this kind. The enormous amount of work necessary in bacteriological proof of carriers in general communities, when no line of typhoid cases points to some individual, is indicated by the report of Müller, who found 165 carriers in 20,019 soldiers examined in two months in the spring of 1916.

As in the cases of typhoid fever, so in carriers, recognition of the condition at once renders preventive measures more efficacious and certain. It is by no means so easy, however, to prevent extension of the disease from carriers, even when they are recognized, for obvious reasons. In the first place, the isolation of carriers even when they prove to be persistent sources of further infection is not legally possible in many communities. The injury they may do to others is manifest but intention in most cases is absent. At most, an individual may be accused only of carelessness, and many measures may be taken to avoid this particular danger. It has been suggested that isolation homes might be provided for recognized carriers, and under certain conditions it might be possible to induce or even legally to enforce residence in such a hospital, where every method that is available could be utilized in an attempt to restore them to their normal harmless condition. In institutions, particularly in asylums, isolation is strictly possible, and such isolation is not only desirable from the standpoint of prevention, but of great advantage, as affording opportunity for the further study of direct methods of attacking this important problem.

It has further been suggested in connection with armies, where the typhoid carrier problem is of great importance, that recognized carriers could be pensioned, subject to certain restrictions bearing on their relation to others.

The best that can be done at present in most instances, when carriers are recognized, is to outline a definite program for the carrier, to enlist his coöperation, and, if possible, to get him form-

ally to agree to follow the rules that are laid down for him. The most important of these rules which the carrier should be urged to follow are, first of all, certain restrictions in reference to occupation. No carrier should engage in the preparation or handling of food in any manner whatsoever. This includes particularly the handling of fruit and vegetables which are eaten raw, the handling of ice, of shell fish and of milk. Second, the carrier should report to the laboratory or public health bureau, from which he received his instructions, at definite intervals, and particularly notify them of any new cases of typhoid fever which occur in his immediate surrounding. Third, he should be urged and instructed to observe strict personal cleanliness in the following ways: he should wash his hands carefully before eating and after defecation; he should use a personal towel; his body linen and bed linen should be sterilized, as in the case of typhoid fever cases, by immersion in an antiseptic solution and by boiling water. His stools should be examined at intervals for the possible detection of typhoid bacilli, but even when several examinations have been negative, the greatest reservation should be made in assuring the individual that he has returned to a normal condition and that he is really harmless to others. The excreta should be carefully sterilized, as in typhoid fever cases, when discharged into temporary receptacles or water closets that are not fly proof.

We have very little knowledge as to what proportion of typhoid carriers who pass into the chronic stage of elimination, that is to say, beyond three months after recovery, spontaneously recover subsequently. It seems certain that recovery may take place at any subsequent period in the history of such an individual, but it is equally certain that certain individuals continue to excrete the microorganism throughout their life, as is evidenced by the detection of carriers for many years subsequent to recovery from the disease. So far, very little progress has been made in accelerating the recovery of carriers, although much information has in the past few years been gained in respect to the condition, which will undoubtedly eventually lead to some specific method of accomplishing this end. At present, cure of the typhoid carrier would seem to be the greatest outstanding problem in connection with typhoid fever. As in our consideration of the carrier condition itself, we may begin discussion of modes of treatment that have been attempted by considering the urinary carriers first.

The focus of multiplication of typhoid bacilli in the case of

urinary carriers may lie, as we have seen, in almost any part of the tract. The original source of the organisms may be in the pelvis of the kidney or in the urinary bladder, or in both. It will not infrequently be found when ureteral catheterization is carried out that the urine from one kidney is sterile, whereas from the other it contains typhoid bacilli. In either case a recent method of treatment which offers certain advantages is the local irrigation with some disinfectants, particularly with silver nitrate in dilute solution. Urotropin (hexamethylamine) has been used for some time during the course of typhoid fever for preventive purposes and later as a means of treating carriers. In some instances carriers have ceased to excrete typhoid bacilli after repeated use of this substance. The majority of investigators, however, agree that urotropin is principally efficacious in limiting the number of the microorganisms during fever and convalescence, but its effect, even if thus limited, is considerable. Certain combinations of urotropin with other drugs would seem to have given better results. Thus hetralin, which contains urotropin in conjunction with resorcin, and borovertin (urotropin plus boric acid) have given encouraging results, according to Ledingham and Arkwright.

Irwin and Houston have reported success in a urinary carrier by the use of vaccines after rendering the urine alkaline with sodium lactate. Stokes and Clarke cured two chronic carriers by the use of urotropin and vaccine.

Possible methods of cure for intestinal carriers have been sought ever since the detection of their existence. Such investigations, although for the most part discouraging, should be summarized in their general features. Surgical interference on the gall bladder has been undertaken in a number of cases on typhoid carriers. It would seem logical to assume that removal of this important metastatic focus might cure the condition for which it seems primarily responsible. Simple removal of gall stones with drainage as in the two cases reported by Dehler, although relieving stagnation of the bile, failed to cure the carrier state. Cholecystectomy was apparently successful in curing the carrier state in Grimme's cases, but failures have been the rule in others that have followed his procedure. This failure seems due to a continued propagation of the bacteria in the bile ducts which become dilated after removal of the gall bladder.

Vaccination has been repeatedly tried as a means of curing carriers, but with very little result. Karell and F. Lucksch claim to have cured thirty-five out of forty-two cases treated in this manner, but in most instances the results by vaccination are

frank failures, as could be imagined when we consider that the individuals so treated are already highly immunized against typhoid fever, as indicated by the presence of antibodies in their circulating blood, and little result could be expected in respect to the localized foci of the disease by still further increasing the systemic resistance to the bacteria. Another method of treatment of somewhat similar nature and of possible future value has been suggested by Herz, who produces the general reaction that may be caused by the injection of any foreign protein by the subcutaneous inoculation of ten cubic centimeters of sterile milk. Such a reaction is accompanied by an increase of leucocytes, and in Herz's cases apparently caused the bacteria to disappear from the gall bladder.

The number, at least, of typhoid bacilli in the intestines of carriers is undoubtedly influenced by the diet. G. Mayer in 1910 suggested that the continued use of milk in typhoid convalescents reduced the number of bacteria and presumably had an effect on the occurrence of carriers. Liefmann in the previous year suggested sour milk for a similar purpose. In this connection it may well be questioned as to whether the rigorous carbohydrate diet, suggested particularly by Coleman, might not be of some service in this connection. This type of diet, which we shall discuss in more detail later, not only apparently spares the body proteins during the course of typhoid fever, but causes the typhoid bacilli to decrease relatively in the stools, as shown by Torrey.

Many investigations in recent years have been concerned with the discovery of a possible type of chemotherapy which would affect typhoid bacilli localized in the gall bladder of carriers. Before proceeding to the experimental studies in this line that have been undertaken, we may refer to certain results of promise in connection with the treatment of human cases of typhoid and of typhoid carriers. Iodine in the form of potassium iodide has been utilized in conjunction with Fowler's solution by Tsuzuki and Ishida with promising results. When these substances are employed during the convalescent period, the bacilli are said to leave the excreta at an earlier period than when no treatment is employed. Kalberlah in a similar manner employed the tincture of iodine in conjunction with charcoal successfully in curing five chronic carriers. Rocek suggests the use of indol, which has an inhibiting action on the growth of the typhoid bacillus in vitro. He finds that normal stools contain indol, whereas typhoid stools do not. The most useful method of investigation for substances of possible therapeutic value in carriers is the typhoid carrier state

in rabbits, to which repeated reference has been made. A considerable number of substances have been tried experimentally in this manner, although so far with very little encouragement. Among them may be mentioned chloroform, employed with negative results by Perusia and by Hailer and Rimpau, but with some success by Conradi,[5] who administered it in milk through the rectum. Other substances that have been employed are methyl iodide and iodoform in chloroform (Hailer and Rimpau), and tincture of iodine (Löwy). Nichols has recently suggested that rendering the bile alkaline by the administration of bicarbonate of soda may diminish the number of typhoid bacilli in the gall bladder, as evidenced by experiments in rabbits. Similar results, it will be recalled, were obtained in urinary carriers by Irwin and Houston. So far, however, no method of treatment of typhoid carriers can be recommended with any confident expectation of result.

THE SUPPRESSION OF TYPHOID INFECTION IN ITS TRANSIT FROM ONE INDIVIDUAL TO ANOTHER

Although the most logical and efficient means of preventing typhoid fever lie in attacks on the restricted sources of infection, it is clear that the great advances in the past have been made by measures directed against the vehicles of transmission of the disease. These measures of prevention center, first of all, in the proper disposal of sewage and the safeguarding of water supplies. Sewage should be discharged in such a way that it may be as far as possible removed from any water source or from any direct or indirect connection with food supplies. In the first place, sanitary toilets should be provided, which simply means that the sewage should enter as directly as possible into the main conduits. The preponderance of typhoid fever in rural communities is due to the unsanitary privy and absence of a closed system of sewage, but even the privy may be rendered less dangerous by careful disinfection of the feces and by screening against flies. The importance of pure water supplies has already been evidenced in the charts in Chapter II, which show the morbidity of typhoid fever in relation to the relative purity of water employed in various communities, and, second, the reduction of mortality produced by changing from a more contaminated to a less contaminated supply. Water when utilized for drinking purposes, or, indeed, for any purposes of human need, should be repeatedly examined bacteriologically and chemically for evidence of fecal contamination. So far as possible

it should be obtained directly from deep-lying springs which are not in connection with ground-water sources. The conduits which lead the water from the springs should be impervious to and protected, particularly at the joints, from seepage from the surrounding soil. When water is obtained from open water ways, such as rivers and lakes, it should be carefully filtered through filter beds or disinfected by the addition of bleaching powder or other disinfectants.

Another important means of prevention lies in the protection of food supplies from contamination either directly from sewage or from carriers. The use of human excreta for purposes of fertilization, particularly when the excreta have been obtained from hospitals, should never be permitted. Oyster beds should never be situated near the mouths of contaminated rivers, and vegetables should be protected in transit from handling, and all food stuffs exposed in open markets should likewise be protected from human contact and, by proper screening, from flies. Another source of possible danger is the handling of ice by carriers, concerning which proper regulations are or should be enforced on railroad trains and steamships. Other possible sources of infection that may be avoided in connection with trains and steamships are the common drinking cup and the common towel, which are fast passing out. Although recent authorities have attached relatively little importance to flies as agents in transmitting typhoid fever, it appears certain that under some conditions they may do so. The systematic destruction of flies would seem desirable for aesthetic reasons and for human comfort, apart from their danger as transmitters of infections. The removal of dung heaps, screening of houses, fly traps and fly papers are therefore judged worthy of all the attention that has been paid them, although the reasons that have stimulated this attention may at times have been over emphasized.

MEASURES OF PROTECTING POSSIBLE VICTIMS OF TYPHOID INFECTION

The last barriers of defense which stand before the individual in protecting him from typhoid infection are certain precautions that may be taken to avoid certain secondary causes that favor the occurrence of the disease. Although these predisposing factors have already been mentioned in some detail, they may briefly be summarized at this point for the sake of completeness. Special care in avoiding sources of typhoid infection should be taken between the years of fifteen and twenty-five, during which

period human beings are most susceptible to the disease. Correspondingly, groups of men composed of individuals between these ages, as in the case of armies, should be treated with additional precautions. Overwork and fatigue should, so far as possible, be avoided and the individual health should be preserved and resistance increased by means of suitable exercises. The time of year in the case of army manoeuvres may be so chosen during the cool months as to avoid the greater dangers of infection during the summer. Proper sanitation of dwellings and pure air in houses should always be considered. In the case of armies, again, the point of intended encampment, particularly in localities in which typhoid fever has been epidemic, should be carefully considered from the standpoint of general healthfulness and the water supply afforded. Proper fly-proof latrines in such army encampments should be provided for reasons already specified. Bathing in polluted streams and in swimming tanks which may be infected by excreta or by carriers should be avoided. Food should be cooked whenever possible, and water boiled when its source is suspected, and particularly when an epidemic of the disease is in progress.

Last and most important of all in individual protection are the matters of personal cleanliness, concerning which many are in ignorance and still others, who are fully informed, careless. Popular education is doing and will continue to do much to correct this frequent predisposing cause not only of typhoid but of other infections. Instruction as to washing the hands before meals is perhaps the most important single principle that should be inculcated from childhood.

All the measures that we have suggested in this section are for the purpose of avoiding ingestion of typhoid bacilli. They represent the last barriers of defense external to the individual, but even when these precautions are neglected, protection against typhoid fever may to a large extent be ensured by proper specific immunization against the disease, as will be fully detailed in the following chapters.

CHAPTER IX

NATURAL AND ACQUIRED RESISTANCE TO TYPHOID FEVER

Typhoid fever is a human disease and does not occur spontaneously in any other animal species. Nor can typhoid fever be produced experimentally in the majority of the lower aniamls. A syndrome resembling human typhoid fever in its terminal aspects may be produced, as we have seen, by the inoculation of rabbits intravenously, and possibly also by mouth, with pure cultures of typhoid bacilli, but the only condition resembling the human disease in practically all respects is the experimental typhoid fever of the anthropoid apes, as described by Metchnikoff and Besredka. Man, moreover, is not only the only animal susceptible to infection with the typhoid bacillus, but is in general under natural conditions rarely protected from it. Some evidences of a relative immunity is evident, however, whenever a group of individuals are exposed to a given source of typhoid infection. A relative insusceptibility or protection is moreover evident when we consider the marked variations in the course of the disease as it occurs in different individuals. In any group of typhoid cases marked differences in the severity of the attack are evident, and even under conditions where the infecting dose must have been relatively the same, as for example when a number of people drink from a contaminated water source or partake of the same dish prepared by a carrier. And not only may an attack of typhoid fever vary in a group of individuals from a mild or abortive attack of fever, lasting from a few days, to a severe and prolonged infection extending over a period of weeks, but certain exceptional individuals may show a reaction to infection with the microorganism which is so mild as to pass unperceived, or be evidenced by a simple gastro-intestinal upset or by headache or malaise, lasting for a few hours. These mild, abortive or unsuspected forms of typhoid fever must, however, be regarded as real instances of the disease, inasmuch as such individuals have been proved to harbor the typhoid bacillus not only in their intestinal canal but also in the circulating blood and gall bladder during and following such an attack. Such

mild cases of typhoid fever represent instances of distinct natural individual immunity or resistance when pains are taken to rule out those individuals who may have suffered from a previous attack of the disease and who thereby have acquired the more general form of immunity following recovery, to which we shall refer presently.

Certain very definite instances of natural immunity have been demonstrated in epidemics. Dennemark, for instance, has reported on 229 individuals who ate potato salad that had been prepared by a typhoid carrier. Twenty-two of these individuals came down within a few days with outspoken and regular attacks of typhoid fever. Fifty-nine of the remaining people had no fever but were found to give a positive Widal, and in four of these individuals typhoid bacilli were found in the stools. Scheller describes a milk epidemic in which seventy-two people over a considerable period of time drank milk contaminated by a carrier. Forty-five per cent of them suffered from typhoid fever within a year, but fifty-five per cent, or forty individuals, remained uninfected. Of these forty individuals that seemed to have been naturally protected from the disease, eighteen were found to have typhoid bacilli in the stools or urine. The isolation of the organism from the latter source indicates that at some period the bacillus must have passed out of the intestine through the circulation into the urine, although no evidence of typhoid fever had occurred. Fornet,[4] in examining the stools of a number of individuals over a period of years, found 187 people with no history of typhoid fever who harbored typhoid bacilli, many of them for a period of months or years. Such individuals are, of course, those that have been denominated healthy carriers and are more fully discussed in our chapter dealing with that aspect of the disease.

We have already remarked on the notable occurrence of typhoid fever among physicians and nurses. They have been shown to be perhaps eight times as liable to the disease as other individuals who do not come into intimate contact with cases of typhoid fever, and yet certain physicians and nurses remain unattacked by the disease in spite of repeated and at times careless exposure. It seems quite possible that the general impression that many physicians have gained that they have become immunized to the fever by absorbing small numbers of typhoid bacilli may have some foundation in fact. Brouardel and Thoinot have referred to this gradual immunization which may also exist in city dwellers as a process of mithridatisation. Such cases as

these may be instances of acquired immunity that have been veiled by an unremarkable or mild attack of the fever. On the other hand, they may represent the natural immunity which is evident, as we have instanced, in every epidemic among certain exceptional individuals.

We shall have occasion in a later section to refer in detail to the localized skin reactions of typhoid immunes to preparations of the typhoid bacillus. The typhoidin test described by Gay and Force has been suggested as an index of protection against the disease. This reaction, which occurs almost invariably in recovered cases of typhoid fever and for a limited and varying period of time in those that have been artificially immunized against the disease, is also found in some ten to fifteen per cent of supposedly normal individuals. In view of our experience with this reaction we may well question whether these people who give no history of a previous attack of typhoid fever and who certainly have never been vaccinated against it may not in fact have recovered from an undiagnosed or unsuspected attack of the disease. We have already reported (Gay and Claypole [3]) the remarkable instance which occurred in a physician's family in which four individuals drank of a contaminated water source and of whom two developed frank cases of typhoid fever within a few days. The other two individuals suffered from malaise and headache for a day at about the time their relatives came down with the fever and had come to regard themselves as having passed through an abortive form of typhoid fever. On testing these four people with typhoidin they all reacted positively. In harmony with the alleged mithridatisation of physicians we may mention that we have records of several physicians who give positive typhoidin reactions with no history of the disease but following years of exposure to typhoid cases.

It has been noted by a number of observers, for example by Louis, Vincent and Muratet, and McCrae, that newcomers in a given locality are more prone to suffer from typhoid than the inhabitants. Country people on coming to the city seem to be particularly prone to infection. This type of infection may be due to carelessness or ignorance as to the proper water supply, but, on the other hand, it may be due to a relatively increaesd susceptibility to unaccustomed strains of the typhoid bacillus, as has been suggested by Vincent and Muratet.

Certain evidence has been given for the existence of a natural racial immunity against typhoid fever, which, however, it seems to us, is in all or nearly all cases better explained on other grounds.

Thus, Vincent and Muratet * would attribute, at least to some extent, the extraordinary freedom from typhoid of the Japanese troops in the Russo-Japanese War to a natural racial insusceptibility. They admit, however, that the occurrence of the disease in childhood may, together with systematic prophylactic immunization, as we would agree, be the more likely explanation for this immunity. Vincent [4] has found that Arabs in Algeria are much less susceptible than the white foreigners to typhoid, presenting proportionately only one-eightieth or one-hundredth as many cases to the thousand inhabitants. Such individuals do not show agglutinins in their blood, but this by no means disproves that they are recovered cases. These observations have been confirmed by Widal.[2]

IMMUNITY FROM TYPHOID ACQUIRED BY RECOVERY FROM THE DISEASE

It was specifically noted by Bretonneau in 1829 that individuals who had already suffered from typhoid fever very rarely again acquired the disease. Gendron in 1834, cites numerous detailed instances of this protection in individuals and families who, although exposed through nursing to acute cases of the disease, are protected from it in virtue of having already suffered from it at some previous time. According to Bartlett, Chomel noted that in one hundred and thirty consecutive cases in the Hotel Dieu, Paris, no individual gave a history of a previous attack of the disease, thus indicating that it did not tend to recur. Similar observations had been made by Nathan Smith in this country, and the combined evidence of these observers has been thoroughly confirmed by all subsequent investigators of this malady.

But protection through recovery from typhoid fever is, as is true of most biological phenomena of this sort, relative and not absolute. Although it may be true that acquired typhoid immunity is less absolute and enduring than the resistance acquired by recovery in other exanthemata (Curschmann), it does not apparently tend to diminish progressively in subsequent years. Piedvache in 1849, gave evidence that the disease might recur in rare instances in the same individual, and a few years later Budd [2] † described four more exceptions to the usual condition of immunity which follows recovery from typhoid. It is interesting to note, moreover, that Budd's explanation of this protection is practically identical with Pasteur's exhaustion theory of im-

* Loc. cit., p. 162.

† Loc. cit., p. 33.

munity and precedes it by some thirty years. Budd would explain acquired typhoid immunity as due to the lack of proper nutritive substance for the self-propagating poison which, to follow his hypothesis, causes the disease, owing to their utilization in a previous attack.

Since these earlier statements and recognition of the possibility of recurrence of typhoid fever in rare instances, numerous estimates have been made as to the exact frequency with which this recurrence actually occurs. It is perhaps generally admitted, as Liebermeister has stated, that recurrences in typhoid are more frequent than in small-pox, measles, scarlet fever and typhus. Estimates of the percentage of cases of recovered typhoid in which another attack may be anticipated have not, so far as we are aware, been given, and would perhaps be impossible to estimate exactly. The figures on which we estimate the liability to recurrence of typhoid fever are based on a past history from individuals suffering from the disease rather than on the subsequent history of recovered cases. In other words, a knowledge of previous typhoid usually rests on information from the patient himself rather than on medical evidence. Estimates of this sort, although they vary considerably in the extreme instances, are on the whole fairly consistent. Drechsfeld estimates that 0.75 per cent of all typhoid cases offer a history of previous attack. Eichhorst in six hundred and sixty-six cases of typhoid fever found a history of previous attack in four and two-tenths per cent. The majority of observers would place the occurrence of a second attack between these two figures: Sinnhuber, for instance, three to four per cent; Curschmann, two and four-tenths per cent; Osler, two and two-tenths per cent (Ruhrah); Fornet, two per cent; Vincent and Muratet, one to two per cent; Seitz, two and fifty-four hundredths per cent. In epidemics where exposure is greater and the infecting dose larger or more virulent, the percentage of recurrences may be larger. Sawyer, and Kelly found that under conditions of massive infection eight and fifteen per cent of their cases, respectively, gave a history of previous attack.

The majority of these estimates were made at a time when the differential diagnosis between typhoid fever and other similar maladies, particularly the paratyphoid fevers, could not have been made on the only correct basis of blood cultures or agglutination tests. They are, therefore, open to the charge of marked incorrectness. The separating out of the paratyphoid cases in the first or the second attack in any individual would on the one hand tend markedly to reduce the percentage of actual recurrences,

but, on the other hand, modern laboratory examinations in cases of mild fever, which might not be suspected of being typhoid, owing to a previous history of that disease, might reveal that the second infection was indeed a recurrence.

This second possibility of a masked or mild second attack is rendered likely by the fact that in the recurrent cases that have been observed the second attack tends to be less severe than the first. Such a condition is not, however, invariable. At all events, it may be accepted, even on the basis of laboratory examination, that recurrences occur and that in some instances even three or four attacks may take place. Recurrent typhoid would, as might be expected, tend to occur at a somewhat later period in life than the ordinary time of occurrence of the first attack. The majority of cases in Eichhorst's series of cases, for example, came between the thirtieth and fortieth year. Recurrences, as already stated, usually occur in epidemics when presumably the infecting dose is larger and more virulent, a fact which again indicates that immunity even of this fairly durable sort is relative and not absolute. It is probable, indeed, that any case of recovered typhoid could be re-infected if sufficiently large doses of the right strain of typhoid bacilli were ingested.

THE NATURE OF PROTECTION AFFORDED BY RECOVERY FROM TYPHOID

The nature of the protection against the disease in typhoid recovered cases is of extreme interest and importance, although as yet by no means fully understood. All present evidence at our command would lead us to regard this protection as cellular rather than humoral in nature. The most important evidence in this regard is the fact that the Widal reaction tends to disappear soon after recovery from the disease, unless the individual remains a chronic carrier, in which case it may or may not be present. Aldershof has found that sixty-nine per cent of typhoid recoveries lose their agglutinins by the seventh month. In eighteen per cent they may remain for years, but finally disappear. Fornet states that the Widal usually disappears in the first months but may be present in a low dilution for several years.

One of the best evidences of the nature of the protection afforded by a previous attack of typhoid fever is the carrier condition in some recovered cases, in which instances individuals continue to harbor and excrete the typhoid bacillus frequently for long periods of time, without themselves suffering from any manifesta-

tions of disease. Such individuals may or may not give a positive Widal reaction. We have, further, frequently stated that there is reason to regard the so-called healthy carriers, who apparently have never had typhoid fever, as having in reality suffered a mild or unperceived attack of the disease, and as having actually had bacilli in the circulation, as well as a residual focus of the micro-organisms in the gall bladder or urinary bladder. These healthy carriers usually give a negative Widal test. The carrier condition, moreover, also presents evidence of the possibility of recurrence of the disease, inasmuch as a few instances have been given in which these people suffer from a generalized reinfection from the typhoid bacillus after years of a relatively normal carrier existence. These facts on the carrier state point to localized but not generalized cellular immunity.

The evidence, then, is that the condition of protection acquired by recovery from typhoid fever is not due to the presence of circulating antibodies, as estimated from the agglutinin titer in such people. Estimations of other antibodies are not so accurate or so circumstantial that any definite statement as to their significance in typhoid recoveries can be made with certainty. There are, however, certain observations as to the presence of antibodies soon after recovery in typhoid fever, which, although not directly indicative of the nature of the long enduring immunity that usually follows this disease, are historically of interest as having led to artificial prophylactic immunization. Stern found that the serum of convalescent typhoid cases and of cases recovered several years previously may protect mice against infection from the typhoid bacillus, and Pfeiffer and Kolle [2] found that the serum of convalescent cases gives rise to Pfeiffer's phenomenon of lysis when injected with the typhoid bacillus in the peritoneal cavity of guinea pigs. These latter experiments led to the work of these observers in protective immunization. There are not, so far as we are aware, any tests as to the protective nature of serum for long periods after recovery from the disease, and such a study would doubtless give information of extreme interest. In comparing the relative inefficiency of typhoid vaccination as compared with typhoid recovery, it is interesting to note that the humoral evidences of protection are more marked following the former procedure than in the latter condition, which is yet another argument in favor of the cellular nature of the stable immunity produced by recovery. It may be, as Jochmann has suggested, that resistance is due to some increased cellular power to produce antibodies rapidly following infection.

THE TYPHOIDIN TEST IN TYPHOID RECOVERIES

Reference has been made under methods of diagnosis of typhoid fever to the use of tests for localized cutaneous hypersusceptibility to products of the typhoid bacillus. Skin tests of this sort are of recognized diagnostic value in prolonged diseases like tuberculosis, but, as we have seen, they occur so late in the course of typhoid fever as to be of little practical value. We shall see at a later point that one of the most important desiderata in connection with artificial immunization against typhoid fever is some method of determining the duration of protection afforded by this means in the individual case. In seeking a method of this sort, Gay and Force have described the "typhoidin test," which would seem at least of value as indicative of lack of resistance to typhoid infection. As a point of departure in establishing the value of a test of this sort it was possible to show that those individuals who are best protected against typhoid fever, namely, typhoid recoveries, give a positive cutaneous reaction. In their early communications Gay and his collaborators (Gay and Force, Gay and Claypole [3]) found that ninety-five per cent of people who gave an unquestioned history of previous typhoid fever (forty-four cases) show a positive typhoidin test. Later figures, both in our hands and in the experience of other investigators, would tend to reduce this figure somewhat, and are in part dependent on changes and improvements in the technique of the reaction itself, which may well be described at this point.

In the original typhoidin test Gay and Force employed a concentrated glycerine bouillon extract of a single strain of typhoid bacillus prepared much as is old tuberculin. This preparation was applied by means of a sterile toothpick to a minute abrasion of the epidermis, and the reactions, in the form of a reddened areola extending for several millimeters outside the abrasion, were read in twenty-four hours, and called positive when they exceeded in diameter by two and one-half millimeters, a control spot of concentrated glycerine bouillon prepared in the same manner but containing no typhoid growth. Estimations of positive reactions are in the majority of cases relatively easy, but, it must be confessed, are open to some subjective error. A number of investigators have been able readily to confirm the contention of Gay and Force that the reaction performed in this manner does occur in the majority of individuals who have recovered from typhoid fever, irrespective of the antecedent date of the disease. On the contrary, it occurs in only relatively few instances in individuals who give

no history of typhoid fever or typhoid vaccination. Thus, Mehler obtained the reaction in eighty per cent of typhoid recoveries, in one case in an individual who had had typhoid some fifty years previously. Gay and Force have mentioned recovered cases of forty and forty-one years' standing. Pulay found the reaction invariably in convalescents and old recoveries. These authors also agree that the reaction occurs only rarely in normal individuals who may be, as we have already suggested, justifiably suspected of having suffered an abortive or unperceived attack of typhoid fever. Austrian and Bloomfield alone obtained the same results in normals as in typhoid recoveries and typhoid vaccinated, owing to the fact that they used by far too large a dose of the typhoidin, a dose, indeed, containing as much typhoid extractives as would be contained in an ordinary immunizing dose of vaccine, and which in itself would be expected to give a local reaction in normal cases.

Several modifications have been made which simplify and render this test far more uniform and accurate. Kilgore has suggested that a more objective reading can be made by the establishment of a typhoid quotient and careful measurements. The measurements, however, of the areola surrounding a cutaneous abrasion are most difficult to determine in some instances, and this improved method is no longer necessary in view of the subsequent improvements that have been made by Gay and Claypole,[3] and Force and Stevens. The latter authors, in particular, have standardized the reaction so that it may now be thoroughly recommended as differentiating typhoid recoveries and typhoid vaccinated from normal individuals. Its significance as indicative of protection against typhoid fever is a matter to which we shall refer at a later place. The modifications of Force and Stevens are, briefly, as follows:

First, employment of an alcohol and ether dried typhoidin precipitated from plain instead of glycerine bouillon as originally employed, which is absolutely dried, kept in sealed tubes, and dissolved in small amounts of carbolated saline for use over limited periods of time.

Second, the use of a polyvalent typhoidin compounded from several strains of typhoid bacilli, chosen as representatives of the antigenic groups described by Hooker.

Third, the *intradermal* administration of a carefully determined, minimal effective dose of the dried polyvalent typhoidin (0.000005 grams in 0.05 cubic centimeters of 0.5 per cent carbolated saline).*

* Through mathematical error the dose was published by Gay and Lamb as 0.00002 grams.

And, finally, the reading of reactions at the end of forty-eight instead of twenty-four hours, which allows the non-specific irritative reactions to subside.

A positive reaction consists in the presence after forty-eight hours of a definite indurated papule surrounded by a reddish areola of at least five millimeters.

With the test in its present form, Gay and Lamb obtained positive results in seventy-five per cent of cases of recovered typhoid, who had suffered from the disease from two to twenty-two years previously. Normals with no history of typhoid or typhoid vaccination gave positive results in a little over fourteen per cent. Alstaedt, who has tested skin sensitiveness by a similar method of injecting a bacillary emulsion intradermally, finds that the reactions are usually positive with a clinical history of typhoid, at least for twenty years.

It would appear from the results of Nichols [2] and of unpublished work of Gay and Claypole [3] with the earlier and now obsolete method that this reaction is not strictly specific in the sense that typhoid recoveries may also react to a solution of paratyphoidin A as well as to a solution of typhoidin. Thus, Nichols found in the case of individuals vaccinated against typhoid fever that sixty-six per cent reacted to paratyphoidin A and no more than seventy-five per cent reacted to typhoidin. He regards this result as militating against the use of this test as an indication of immunity against typhoid, because it may be generally accepted, as we shall later see, that typhoid vaccination does not protect against the paratyphoid fevers.* In the case of typhoid recoveries, with which we are for the moment primarily concerned, we have also found that some reacted when tested to paratyphoidin A as well as to typhoidin. Only half as many, however, reacted to the first solution as to the second, and in every instance but one the reaction was distinctly less with the paratyphoidin than with the typhoidin. The only individuals that showed a more marked reaction to paratyphoidin A were two who had suffered from well authenticated cases of paratyphoid A fever. It is probable that decisive information on this point will be obtained when a series both of paratyphoid and typhoid recoveries are tested with the two solutions. Similar doubts of the prognostic value of the typhoidin test as indicating protection against typhoid have also been raised by Meyer and Christensen, who in several extended articles have painstakingly

* Similar reasoning would require that the serum of cases of typhoid fever should never give agglutination reactions with B paratyphsus alpha; we know, however, that such reactions occur not infrequently.

repeated our animal experiments successfully, but have not been able to agree with our conclusions. Gay and Claypole [3] had endeavored to explain the mechanism of the typhoidin reaction and incidentally to show the relation of a positive reaction to a condition of immunity by testing a number of vaccinated rabbits which were subsequently tested for their resistance against becoming carriers, as already described. We found that fewer animals among those which became carriers on intravenous injection gave positive typhoidin tests than among those which resisted such an injection, and thereby concluded that there was some relation between the two results. Meyer and Christensen amplify these results but draw the conclusion that since they are able to produce carriers at all in animals that give a positive typhoidin test, the test is no indication of protection. This failure to appreciate the essential relativity of biological phenomena is unfortunately rather common. It is not to be supposed that any form of immunization, even the most durable one afforded by recovery from typhoid fever, affords absolute protection. It has, indeed, been shown that there are a certain percentage of recurrences of the disease, and, as we have already stated, we are convinced that under proper conditions any recovered typhoid case could be artificially infected with typhoid fever. The value of the typhoidin test is principally when negative, as indicating a failure to react sufficiently to typhoid extractives, rather than when positive, as a measure of the degree of protection against typhoid fever. This conception of its limitations in no way interferes with its value in connection with typhoid vaccination, as we shall see.

CHAPTER X

ARTIFICIAL IMMUNIZATION AGAINST TYPHOID FEVER

Beumer and Peiper were the first to appreciate the possibility of an active immunization against infection with the typhoid bacillus. In 1887 they were able to prove that mice that have recovered from a non-fatal infection with living typhoid bacilli are frequently protected against subsequent, larger, and usually fatal doses of the same organism. In their most successful experiment they found that the best results were obtained by the gradual increase in dosage on successive inoculations, and they further suggest that it may be possible to immunize by means of sterilized cultures, which, as had already been shown, contain the toxic principle of the typhoid bacillus. They raise the question as to whether it might not be possible to immunize human beings by means of gradually increasing amounts of such killed cultures. In the following year Chantemesse and Widal, following the work of Salmon and Smith on hog cholera, and of Roux and Chamberlain on malignant edema, found that they could protect mice against infection with living typhoid bacilli by means of sterilized cultures of the organism.

The practical application of these experimental results in animals to the prevention of typhoid fever in human beings did not come until eight years later, following the discovery of the lysins by Pfeiffer. It was A. E. Wright, who, in a preliminary publication in 1896 followed by a fuller account by Wright and Semple in the beginning of 1897, first outlined a method of immunizing human beings against typhoid fever.* Wright grew cultures of the typhoid bacillus in bouillon for two or three weeks and then killed them by heating to 63° Centigrade for an hour, and preserved them with 0.5 per cent phenol (carbolic acid). These vaccines were then tested for sterility and their toxicity carefully standardized by determining the minimal lethal dose for guinea pigs; the dose

* Those who are interested in a polemic regarding the questioned priority of Wright's work over that of Pfeiffer and Kolle are referred to articles by Friedberger and by Wright,[2] published in the Centralblatt für Bakteriologie, I. Abt., Vols. 44 and 46.

chosen for injection in human beings was measured by this toxicity for animals. Wright further utilized a method of counting the number of the bacteria in the preparation employed by comparing their number in a given dilution when mixed with a suspension of red blood-cells, the number of which could be accurately determined. The dose of bacteria usually employed was from 750 to 1,000 million.

In the same year (1896) Pfeiffer and Kolle, following their work on the lysins in convalescent typhoid cases, immunized a few men and then estimated that protection had been produced from the increased content of their serum in agglutinins and bacterial lysins. They employed agar cultures of an avirulent strain of the typhoid bacillus suspended in salt solution and killed by heating to 56° Centigrade. An amount of this suspension, corresponding to one-tenth of an agar culture or something like two milligrams, was usually given on the initial injection, which was, as a rule, the only one. It is frankly admitted that the symptoms produced by this amount of culture were severe, and the method has since been modified in several ways to avoid these symptoms without essentially changing the principle involved.

So much for the first two communications on typhoid immunization in human beings. They form the groundwork on which subsequent methods of vaccination against typhoid fever have been built. The various methods that have since been advocated are numerous. Metchnikoff and Besredka estimate that at least twenty different methods of vaccination have been described and advocated. Friedberger,[2] in his systematic review on typhoid immunization, enumerates twelve recognized methods. Paladino Blandini has actually attempted to test the comparative immunizing value of seventeen preparations in guinea pigs. It is not our purpose to describe all these methods in detail, and the reader who wishes further information on them may consult the systematic description of Friedberger or of Fornet [2] in regard to them. It will be well, however, to outline the most important of these methods as evidence of the scope that the investigation has taken in perfecting this type of immunization, and as indicating the tendency which would seem to be leading to its gradual perfection.

PREPARATIONS OF THE TYPHOID BACILLUS THAT HAVE BEEN USED AS VACCINES

Killed Cultures of the Typhoid Bacillus.—We have already mentioned that the first two preparations, those of Wright and of

Pfeiffer and Kolle, consist essentially in killed cultures, the one a bouillon culture, and the other a suspension of an agar culture. These two original methods have been followed by many modifications. Thus, Loeffler took advantage of the fact that ferments, when dried, resist heating to a considerable degree without deterioration, and, regarding the antigenic property of the bacillus as ferment-like, he dried suspended agar cultures of the microorganism and then heated them to from 120° to 150° Centigrade. These dried cultures were then pulverized and used in weighed amounts for immunizing animals. He states that such a culture has lost little of its property to produce antibodies. Friedberger and Moreschi use a similar dried and heated culture in an amount corresponding to 1–4,000 oese in immunizing human beings. It should be noted at this point that the method currently employed of determining the immunizing value of these preparations lies in an estimation of the antibodies (agglutinins, lysins, etc.) produced. As we shall later have cause to consider, these estimations offer an indication rather of the reaction of the animal body than a sure means of determining the degree of protection that has actually been afforded.

As we shall see in a moment, the use of living instead of dead cultures has been warmly advocated by certain observers, and their assertions have apparently convinced several who are not quite willing to adopt such preparations owing to their possible danger, although they endeavor to approach them as far as possible without actually using living microorganisms. It is apparently now the consensus of opinion that bacterial cultures are more antigenic when employed as nearly as possible in their living unaltered condition, and that heat in particular tends to alter or destroy essential, characteristic, antigenic properties. Several methods have been advocated for avoiding or obviating so far as possible the destructive influence of heat, and at the same time killing the bacteria. Leishmann advocates killing the typhoid bacillus at 53° Centigrade instead of at 56° or 60° Centigrade. Vincent,[2, 3] while fully recognizing the superior value of living cultures, regards their use as dangerous, and therefore kills the vaccines that he employs by means of ether. As will be later mentioned, we have used alcohol for the combined purposes of killing the typhoid bacilli and accelerating their flocculation and drying. Levy and Bruch killed their preparations by shaking the microorganisms in a medium containing galactose, and find that organisms prepared in this way immunize guinea pigs as well as the living cultures, and that these two preparations are far su-

perior to heat-killed cultures in corresponding amounts. Fornet [2] regards the unpleasant effects that are produced by the heated vaccine as due not only to the heating itself but also to the presence of a large amount of albumin in the culture medium. He therefore grows his microorganisms in a medium containing only a small amount of peptone and kills them by heating to 55° Centigrade for fifty-five minutes. Courmont and Rochaix killed their preparations by heating to 53° Centigrade. Nicolle, Conor and Conseil heat their bacteria to 55° Centigrade for forty-five minutes, and then to 52° Centigrade for thirty minutes more. Wassermann [2] insists that the antibodies produced by typhoid bacilli heated to 53° Centigrade are not markedly better than when they are heated to 56° Centigrade. Widal [3] believes that considerably higher temperatures may be used without harming the vaccine. Renaud [1, 2] has advocated the use of ultraviolet rays to kill the bacteria. Kisskalt [2] kills and preserves his cultures by the addition of phenol alone, a method which had previously been employed for dysentery vaccine by Gay. Nicolle and Blaizot have killed their vaccines by the addition of sodium fluoride, and Ranque and Senez [1, 2] have described vaccines which have been killed and preserved by the addition of iodine. Achard and Foix mix their vaccine with oil before administering it.

Bacterial Extracts.—In addition to killed cultures of bacteria, numerous extracts and preparations derived from them have been advocated for the purpose of immunization. Hahn has recommended the extract obtained from masses of bacteria by means of the Buchner press. McFadyen and Roland utilized liquid air as a means of killing bacteria and obtained from them an extractive substance. Neisser and Shiga have utilized free receptors obtained by autolysis of bacteria at body temperature in salt solution. Wassermann [2] has suggested a similar method with the autolysis produced by distilled water. He subsequently dries the extract obtained in this way and uses it as a vaccine powder (Impfpulver). At a later place we shall refer to the form of dried sensitized vaccine which our personal experiments have led us to recommend for immunization against typhoid fever. Dried vaccines have also been used as thoroughly antigenic and as giving better methods of estimation by Wilson and Dickson and by Brown. Brieger and Mayer have used a watery, filtered extract of shaken bacteria. Bergell and Meyer have used an extract of dried bacteria obtained by treating them with dilute hydrochloric acid.

Various so-called soluble toxins of the typhoid bacillus have

also been suggested for immunizing purposes by Chantemesse,[3] by Werner, and by Rodet, LaGriffoul and Wahby. The extract of bacteria obtained by the method of Jez has also been suggested.

Living Cultures of the Typhoid Bacillus.—Living cultures of the typhoid bacillus, usually more or less modified in their pathogenicity, have been warmly advocated by certain observers as producing the best immunizing preparations similar to those that have been employed in dealing with other diseases, notably in cholera (Strong). Castellani [4] uses an avirulent strain of the typhoid bacillus in the form of recent bouillon cultures which are then partially killed by heating to 50° Centigrade for one hour. Such a modified culture produces rather severe local and general symptoms, but when given twice would, to judge from Castellani's results,[5] produce a most satisfactory degree of immunity, which apparently has lasted in a number of cases on which he reports for at least four years. He suggests, as an alternative, that the first injection may consist of a killed culture followed by a living culture on the second inoculation. In addition to the superior immunizing properties of the living culture, it is also pointed out by Fornet [2] that the killed cultures in a given dose give more reaction because the split products of proteins, which are recognized to be toxic, are liberated by heat. Living cultures have also been employed by Pescarolo and Quadrone. The form of living cultures which has been advocated by Metchnikoff and Besredka will be considered under the next heading. As has already been mentioned, living cultures are generally admitted to be of superior immunizing value by many who are not willing to adopt them, owing to the real or fancied dangers coincident with their use, and this has led to an attempt to approach the condition of living bacteria without actually employing them.

Sensitized Cultures of the Typhoid Bacillus.—Active immunization by means of sensitized vaccines, that is to say, by cultures that have been first treated with an immune serum and then killed, was introduced by Besredka [2] in 1902. This method is not infrequently referred to as serovaccination, but it differs from the method properly called serovaccination suggested by Leclainche in swine erysipelas and by Calmette and Salimbeni in plague, in that the excess of immune serum which these authors used is removed from the treated bacteria. It was found, as Besredka notes, that this excess serum tends to produce simply a passive immunity instead of the active immunity which is produced by the cultures treated with immune serum, and washed. Apart from his original experimental work, Besredka did not

deal with the practical aspects of sensitized vaccines until the experimental work on typhoid fever in apes was taken up by him in collaboration with Metchnikoff in 1911. In the meantime, however, sensitized vaccines had been tried out apparently with considerable success in at least three instances. Marie had been able to utilize the principle in treating rabies virus, Dopter in vaccination against dysentery, and Theobald Smith in a similar way found that he could produce active immunity by a balanced mixture of diphtheria toxin and antitoxin. This method of active immunization against diphtheria by a balanced (sensitized) mixture of toxin and antitoxin has recently been applied to human beings by von Behring. The principal advantages of this method, as originally claimed by Besredka,[2] are, first, it produces little or no violent reaction on inoculation in instances in which the untreated bacteria themselves are distinctly irritating, as for example with Bacillus pestis. Secondly, it gives rise to an immediate though transitory passsive immunity. Thirdly, it produces, eventually, an active immunity which is as enduring and as rapidly formed as when untreated bacteria are used. The second contention as to the establishment of an immediate passive immunity must, we think, be distinctly questioned in view of subsequent work.

Not a little experimental work was done with sensitized typhoid vaccine before the work of Metchnikoff and Besredka, which will be taken up later. Paladino Blandini made a very careful study of seventeen different typhoid vaccines, comparing their relative immunizing properties. His experiments were carried out on guinea pigs, which were treated by the various preparations and subsequently given an intraperitoneal dose of living typhoid bacilli. The vaccines tested include small doses of living cultures; killed cultures prepared after the method of Pfeiffer and Kolle, and of Wright; several "soluble toxin preparations" of the typhoid bacillus; nucleo-albumins; and extracts of the typhoid bacillus prepared in different manners. Compared with these preparations was the sensitized vaccine employed by Besredka, and Blandini was able to demonstrate that the latter was by all means the most protective. Not only were guinea pigs protected for at least four months, but it was found that their serum, which contains sensitizers, also protects normal animals against infection.

Ardin-Delteil, Negre, and Raynaud find that the use of sensitized typhoid vaccine in rabbits and human beings gives rise to relatively small amounts of agglutinins, but the bactericidal

properties of the serum of those treated in this manner are much higher than of those treated by the ordinary cultures. This failure of sensitized or agglutinated cultures to produce potent antibodies has also been noted by Neisser and Lubowski, by Pfeiffer and Bessau, and by Broughton-Alcock. A number of authors have studied the antibodies produced by immunizing animals and human beings under identical conditions with sensitized or with non-sensitized vaccine. Among them may be mentioned Garbat and Meyer, Garbat,[2] Gay and Claypole,[3] Liebermann and Acel,[2] Grobl and Hever, Stoner, and Meyer and Kilgore. The majority of them agree that sensitized vaccines in general produce less potent agglutinins but better sensitizers or fixation antibodies than the untreated vaccines. Garbat and Meyer, further, have found that the serum of animals immunized with sensitized cultures protects passively better than the corresponding sera from animals that have been treated with plain cultures.

In 1911 Metchnikoff and Besredka published their very important work on experimental typhoid fever in anthropoid apes. Having shown that a disease syndrome, which we have considered elsewhere in detail, could be produced in these animals in all respects similar to human typhoid fever, they then proceeded with a limited number of animals to make comparative tests of the immunizing power of different vaccines. They found, in brief, that Vincent's polyvalent vaccine and a dead sensitized vaccine prepared by the Besredka method both failed to protect monkeys under the conditions of their experiments against subsequent infection with typhoid bacilli, but a few animals were protected perfectly by previous treatment with *living* sensitized cultures. From their protocols they draw the conclusion that the living sensitized vaccine is the only suitable means of preventing typhoid fever, a conclusion which, in view of the uniformly favorable results that had been already obtained in protecting human beings by various killed vaccines, would seem unwarranted. Both Vincent,[4] and Gay and Claypole [3] have criticized the necessarily limited number of the animals in their experiments and the sweeping conclusions they have drawn from them. But, although not all their conclusions would seem justified, it would certainly seem demonstrated from the results that they and their followers have reported (Broughton-Alcock, Metchnikoff and Besredka,[2, 3] Besredka,[3]), that the living sensitized vaccine gives little or no reaction, does not set up a carrier condition, and actually protects men very well against typhoid infection.

Gay and Claypole [3] in an extended series of experiments have

endeavored to test the comparative immunizing value of a number of different preparations of the typhoid bacillus. Their method consisted in determining the relative percentages of rabbits immunized by different methods that could at subsequent intervals be infected with living typhoid bacilli in such a manner as to produce permanent carriers. Under the conditions of their experimentation, employing cultures of the typhoid bacillus grown for many generations on rabbit blood agar, they were able to produce carriers almost invariably in normal control rabbits. As a result of these comparative experiments very distinct differences were found in the immunizing value of different typhoid preparations. In successive series of experiments it was shown, first, that untreated bacteria killed and precipitated by alcohol, dried, ground, and employed in weighed amounts, do not protect as well as typhoid bacilli that have been sensitized by a strong immune serum, washed and subsequently treated in the same manner. Second, it appears that in the case of unsensitized, dried bacteria the sediment of bacterial bodies freed from the supernatant endotoxic fluid, as prepared from these dried cultures, contains the immunizing principle almost in its entirety. The sediment of either sensitized or unsensitized cultures protects not only better than the supernatant fluid from these sediments, but actually better than the whole unseparated mixture; in other words, the supernatant extractive would seem actually to inhibit immunization. Finally, alcohol-killed, sensitized cultures protect almost as well as living sensitized cultures (Metchnikoff and Besredka), and the sediment of alcoholic, killed, sensitized cultures protects better than living sensitized cultures.

Another matter of considerable importance in the choice of vaccines to be utilized in preventing typhoid fever would lie in a decision as to whether a monovalent or a polyvalent vaccine is the more efficient. Most of the large armies, which represent the bulk of material available for statistics in typhoid vaccination, have used a vaccine containing a single strain of typhoid bacillus, as for example that employed in the English and the American armies. The idea of employing a mixture of several strains of the typhoid bacillus had been suggested by Wassermann in 1903 and later approved and carried out by Vincent in the immunization of the French army. The idea of both these observers has been that since typhoid bacilli vary in their known reactions to immune serum and in their ability to produce immune sera on inoculation, they must vary in antigenic properties, and, conversely, that an individual immunized with a single strain would not be so well

suited to combat an unknown infecting strain, unless a dominant strain had been used for immunization, which might be expected to produce antagonism to any variety of typhoid bacillus that might be encountered. Vincent [5] has further expressed the opinion that bacteria from the locality of exposure should be the ones chosen by preference in producing prophylactic vaccine, and Vincent and Muratet have given evidence for believing that a recurrence of the disease in a given individual may be due to the encountering of an organism differing antigenically from the one that gave rise to the first illness. It is with a similar viewpoint that Gay and Claypole,[3] Hatchell and Stoner, and others have also recommended a polyvalent vaccine.

The choice of polyvalent vaccine was, however, it must be confessed, more or less empirical until very recently. It remained for Hooker, and independently for Weiss, to demonstrate that typhoid bacilli may actually be divided into definite groups on the basis not only of cultural but more particularly of their antigenic peculiarities. Their work would seem to indicate, first of all, that it is not safe to trust to immunity produced by a single strain of typhoid bacillus, and, second, that not only should several strains be used in compounding a vaccine, but that recently isolated strains are probably more antigenic than those that have grown for a long period of time on culture media.

It may well be questioned why further modification of typhoid vaccine should seem necessary in view of the extremely good protective results that have already been obtained in certain large groups of individuals, as in the American army, in which latter case a single strain of an old stock culture of vaccine has been employed. Since typhoid immunity, either artificial or acquired by recovery from the disease, can never become an absolute and invariable condition of resistance, why should further refinements in a process which seems so well perfected be attempted? These remarks, of course, apply not only to the question of polyvalency, but also to the various procedures, such as sensitization, various ways of killing the bacilli, and the like, that have been employed in preparing the numerous types of typhoid vaccine. The only answer to such questions is and must ever remain that theoretical considerations based on the understanding of underlying principles will ever precede all practical advances. And, again, that advances lie not so much along paths that have already been trodden as in unexpected ways. No investigator in his theoretical studies can ever afford to let well enough alone.

METHODS OF ADMINISTRATION OF TYPHOID VACCINE

Typhoid vaccines are ordinarily and preferably administered subcutaneously. Injections into the muscles should be avoided, as they give rise to more unpleasant symptoms than when the bacilli are deposited in the subcutaneous connective tissue. Several attempts have been made to demonstrate that vaccine could be administered by the mouth and an equal degree of immunity thereby produced. Thus, Kutscher and Meinicke tried to immunize guinea pigs in this manner, but were unable subsequently to demonstrate antibodies in their blood. Wright found that the administration of from one to fifteen cubic centimeters of his vaccine by the mouth gave rise to no unpleasant symptoms in those who had previously been immunized by the subcutaneous method, but it produced diarrhea in an unvaccinated individual, and although the bactericidal property of the blood was increased for a short period of time after such immunization, this method of administration was abandoned. Vaccination per os has recently been suggested again by Tremolières, Loew and Maillart, who advocate giving the vaccine in the form of pills. They state that this administration gives rise to no reaction, but they give no evidence of its value in producing protection. Nicolle, Conor and Conseil injected their vaccines intravenously and found that antibodies were produced rapidly even after a single injection. Friedburger and Moreschi have used a similar method. These latter methods of administration intravenously or by the mouth are no longer, however, seriously recommended by anyone who has had much experience with preventive inoculation.

The doses employed in immunization have varied in the hands of different experimenters and have, in general, tended to increase in number and amount of bacteria employed. Whereas the first advocates of typhoid immunization, Wright and Pfeiffer and Kolle, used only one or two injections, the number has subsequently been increased by most observers to three or four. The size of the dose is generally increased on successive inoculations, beginning with a dose of 125 to 500 million of bacteria, which are estimated by one of several methods; by counting the bacteria in a blood counter, or by comparison with red blood corpuscles, or, better still, by utilizing weighed amounts of dried bacteria. The most frequent doses that have been used when three inoculations are given have been 500, 1000, and 1000 million, but the total number of bacteria injected throughout the course of treatment would seem to be more important than the number of injections (Vincent and

Muratet, Landouzy). Vincent estimates that at least 2000 million should be used in a course of treatment, and the number of injections may be diminished from the four which he originally advocated to two, provided the total number of bacteria injected remains the same. In the British army up to the time of the present world war it was customary to give only two doses of vaccine, which were increased to three in the American army with distinctly better results. We understand that the number of injections has since been increased to three in the English army as well. In France four and even five injections have been given, or, as mentioned, the same amount in two or three injections. We personally have recommended three injections of 800 million bacteria or one-tenth of a milligram, but have recently been led to advocate increasing the number of injections to four or the size of each dose, owing not only to the occurrence of a few cases of typhoid among civilians that had been vaccinated, but also to the failure to obtain positive typhoidin tests after three vaccinations in a few cases, although it almost invariably has appeared when a fourth injection was subsequently given.

The intervals of time which are allowed to elapse between injections are, again, a matter of importance. It has been customary to allow from seven to ten days to elapse between injections, based on no particular reason that we can find except that such a period would seem to represent the maximum of antibody formation following a single injection of antigen. As we have and shall repeatedly mention, we believe that the antibodies in themselves are no sure measure of the degree of protection, but even if they be taken as an indication of the degree of reaction produced, as they probably are, it may be shown that the final results in antibody formation following a series of injections can be obtained fully as well by repeating them at shorter intervals. These facts have been clearly demonstrated in animals by the work of Fornet and Müller, and Bonhoff and Tsuzuki, which has been further amplified by the work of Gay and Fitzgerald. In immunizing rabbits against the typhoid bacillus, it was further shown by Gay and Claypole [3] that an equally durable grade of resistance could be produced irrespective of whether the vaccine was given daily or at three day or seven day intervals. We have, therefore, practiced prophylactic immunization in man by inoculations on alternate days rather than at longer intervals, a procedure of considerable value not only in assuring more rapid protection, but particularly in such emergencies as when troops are rapidly mobilized.

THE IMMEDIATE EFFECTS FOLLOWING ANTITYPHOID INOCULATION

The injection of typhoid bacilli or typhoid vaccine in human beings may produce a train of symptoms, which in mild degree suggest those of typhoid fever. These symptoms have, indeed, in certain hands, with certain types of vaccine, been so severe as to militate greatly against the widespread adoption of the method, although not in themselves of any serious import. As we shall presently show, vaccines vary considerably in the severity of the symptoms which they produce, and it becomes a matter of no little importance, whenever it can be done without detriment to the prophylactic results which are aimed at, to employ a type of vaccine giving the least possible untoward effect. It is extremely difficult to correlate from symptoms described or not described, the experience of various authors, not only with different vaccines but with any given vaccine. The greater part of our information in reference to typhoid vaccination comes, as already stated, from the immunization of troops, young and healthy men, whose very choice of a profession indicates that they would be inclined to minimize personal discomfort. It is probable also that even those individuals who might be inclined to notice subjective symptoms are not encouraged to do so, as civilians might be in the hands of a family practitioner. There has been no agreement in the description by various authors as to what constitute mild, moderate and severe symptoms, which further complicates any attempt to estimate the actual results that may be expected.

The symptoms following antityphoid inoculation may be divided into local and general. The local reaction consists in a reddened induration or at times an edematous swelling with more or less pain, extending from the point of inoculation for from a few centimeters to the entire length of the arm. The general symptoms, any or all of which may occur after inoculation, comprise a rise in temperature, which may reach 101° or 102° F., malaise, dizziness, headache, vomiting, and general mental dullness and lassitude. Insomnia has also been encountered in some cases. Symptoms of this sort have been noted following immunization since the observations of Pfeiffer and Kolle to the present time. Apart from individual variations in susceptibility to the injection not only of typhoid vaccine but of any foreign protein, may be noted certain general conditions which would seem to offer peculiar susceptibility to unpleasant reactions. It has been found, for example, that severe reactions are more likely to occur in tuberculous individuals and in those suffering from albuminuria and nephritis, e. g. Ton-

nell, and Maurange. Maverick, Force and others have noted that recovered typhoid cases react more markedly than normal individuals. Patients in the incubation period in typhoid may react violently to inoculations, although this very reaction may be followed by an aborting of the disease (Vincent and Muratet). Other conditions which predispose to more severe reactions are fatigue and overwork, or a heavy meal a short time preceding. Any acute disease, such as grippe or malaria, may accentuate the effect (Dziembrowski). Certain advanced organic diseases, arteriosclerosis, diabetes, nephritis, myocarditis, or chronic pleurisy, are practically the only conditions which serve as distinct contraindications to vaccination. In general, the second and third injections, possibly owing to the larger amount of vaccine usually employed in these injections, give rise to more symptoms than the first. Children usually react less markedly than adults with corresponding or even with the same dose.

It is extremely difficult, for reasons that we have stated, to estimate the relative toxicity of any given vaccine in respect to others that have been employed, except in those rare cases where some individual has tried a number of vaccines in a comparative manner. It is pretty well admitted, both on the evidence of the authors themselves, of Friedburger,[2] and of others, that the Pfeiffer and Kolle agar vaccine cultures, killed by heating to 58°–60°, produce rather severe local and frequent general symptoms. Boehncke compared the Pfeiffer and Kolle vaccines with the vaccines of Wright, of Russell (U. S. army), and of Vincent. He found that the Pfeiffer and Kolle vaccine was the most toxic and that Vincent's was the least toxic of the other three. This latter conclusion agrees with observations by Louis and Combe, who obtained little reaction with Vincent's vaccine. The United States army vaccine, particularly when employed in civilians (Hartsock, Albert and Mendenhall), apparently gives rise not infrequently to distinctly unpleasant symptoms, although their occurrence is minimized by the majority of army officers who have reported their observations. The army vaccine is by no means peculiar in this respect, and, indeed, has been claimed by army officers to be less provocative of unpleasant results than other similar vaccines of this type simply prepared from heat-killed bacteria grown on agar. The untoward symptoms may to a large extent be avoided by injection late in the afternoon, by a light diet, and by avoiding injection following periods of fatigue. Whatever reactions do occur are usually more marked on the second injection which is normally twice as large as the first.

Many efforts have been made, however, to avoid the toxic element inherent in vaccines of the ordinary type, either by removing some toxic substance present in the culture media (Fornet [2]), or the endotoxins of the bacteria (Johan), or, more particularly, by the use of sensitized vaccines, the properties of which have already been described. Sensitized vaccines when recommended should never, however, be recommended simply on the ground of producing less reactions, because none of the reactions that have been discussed are sufficiently severe to contraindicate the use of any vaccine that gives rise to a durable type of immunity. There are, however, a number of reports which would seem definitely to indicate that the original contentions of Besredka as to the peculiar inoffensiveness of sensitized vaccines are justified in practice. Broughton-Alcock and Garbat,[3] for example, have emphasized this point, and the Gay-Claypole vaccine, which is not only sensitized but is also free from endotoxin, has shown peculiar freedom from unpleasant results. The freedom from symptoms attending the prophylactic use of this vaccine has already been reported by Force.[2] In a more recent summary comprising 4,845 inoculations, Force has found that slight local reactions were produced in only twlve per cent and severe reactions in three and six-tenths per cent. The general symptoms were slight in 24.5 per cent and severe in only two and four-tenths per cent. The criteria on which the degrees of reaction are estimated are as follows:

A. Slight local reaction: redness of the arm from 40 to 75 mm. in diameter.

B. Severe local reaction: redness of the arm over 75 mm. in diameter.

C. Slight general reaction: headache, lassitude, disturbed sleep, loss of appetite, a rise in temperature to 38° C.

D. Severe general reaction: chill, diarrhea, a rise in temperature above 38° C.

Stoner and Kilgore [2] do not find any more severe reactions from the ordinary army vaccine than from sensitized vaccines, but in the particular series of cases with which they dealt the army vaccine produced few if any of the more severe symptoms which have been noted by other observers. At all events, it may certainly be stated that it has never been found that sensitized vaccines do produce the severer reactions, which have sometimes been caused by unsensitized vaccine.

The reaction on the part of the blood cells to antityphoid inoculations has been particularly studied in Germany during the

present world war, and it has been found that in a general way the leucocyte picture resembles the one characteristic of typhoid fever. There is general agreement that each injection is followed by a leucopenia (Matthes, Glinchoff, Ziersch, Courmont and Rochaix [2]), which is characterized by a relative increase in lymphocytes (Labor; Lipp; Schneider; Hage and Korff-Petersen). Ickert reports that eosinophiles are for a time decreased following inoculation, but Lipp, Hage and Korff-Petersen, Ickert and Labor all find that the eosinophiles are ultimately increased and may remain so for several months following injection. A decrease in the number of red blood corpuscles has also been noted by one or two observers (Tonnel).

It may be recalled that the criterion on which Pfeiffer and Kolle based their expectation that a protection against typhoid fever would follow the inoculation of killed typhoid bacilli in human beings, was an increase of the lytic substances for the typhoid bacillus formed in the blood serum of individuals that had been treated in this manner. The subsequent years of fruitful study of antibodies, the agglutinins, the lysins, the tropins, the fixation antibodies, and the like have yielded an enormous number of facts of theoretical and of practical importance. We know that the presence of antibodies to any foreign protein substance in an animal indicates that that particular animal has reacted in a specific manner to the protein or bacterium in question. We know that these antibodies are concerned directly or indirectly in certain ways in the actual protection of that particular animal against such a protein, if it chances to be, as in the case of a bacterial protein, a cause of possible danger to the individual. We are far, however, from knowing the exact mechanism of action of these antibodies, or which of them are more particularly concerned in the protection itself. In other words, the estimation of any given antibody indicates that the animal furnishing it has undergone infection or inoculation with the protein in question, but in reality, according to later conceptions is no true indicator of the degree of protection that is afforded against the harmful effects of the particular protein. This would also seem true in respect to resistance against the typhoid bacillus, which, as we have already stated in our consideration of immunity acquired by recovery from typhoid fever, must be regarded as cellular rather than humoral in nature. Antibodies have been shown to exist following artificial immunization against typhoid fever with various typhoid vaccines. The agglutinins, fixation antibodies and sensitizers have in particular been studied. We

know that agglutinins are produced in the majority of instances in individuals who have undergone antityphoid inoculation. Wade and McDaniel, for example, estimate that some ninety per cent when tested a few weeks after completing treatment will give a positive Widal reaction. Dakeyne found eighty per cent of positive results within the first year. Klien has found that the Widal is highest about two months after inoculation, and these findings are in agreement with those of Bronner, Howell and Ziersch. Wade and McDaniel found that in the majority of cases the agglutinins disappeared in from six to twelve months. In their series they were positive in only sixteen per cent at the end of six months and in 11.7 per cent at the end of a year. Other observers, for example Dreyer and Inman, found the Widal positive in all cases at the end of eight months after two injections of vaccine. Discrepancies of this sort in findings are dependent on several factors: first of all, the degree of dilution in which the serum would be expected to give a positive reaction to the typhoid bacillus; secondly, the amount of vaccine employed in immunizing; and, thirdly, the type of vaccine itself, for, as we have already stated, sensitized vaccines are usually characterized by a failure to produce as strong agglutinins as unsensitized vaccine.

The evidence, on which we have based the assertion that the presence or the intensity of the agglutinins in immunized individuals is not a correct indication of the degree of resistance of the individual concerned, is briefly as follows. In the first place, the agglutinin test is usually negative within a short period of time in cases of recovered typhoid fever, than whom no individuals show greater protection against this disease. The Widal usually becomes negative in a few days or months after recovery, and, at all events in very rare instances, remains positive for the years during which this resistance to typhoid infection is known to exist. The agglutinin test, moreover, is either negative or weak very frequently after complete immunization with sensitized vaccine, as compared with corresponding doses of unsensitized vaccine, and yet we know from the experiments of Gay and Claypole [2] that rabbits treated with the sensitized vaccine are more efficiently protected than the ones treated with unsensitized vaccine in corresponding doses, and become infected irrespective of the degree of the agglutinin titer of their serum. It has further been shown by Besredka,[3] Sawyer,[4] and others that sensitized vaccines may be expected to protect human beings against typhoid fever at least as fully as unsensitized vaccine.

It has been shown by a number of observers that the presence of antibodies against the typhoid bacillus is no certain indication of protection against infection with this microorganism. Thus, Marx found that a technician that had been immunized against typhoid and whose serum destroyed the typhoid bacillus in high dilution, was three months later infected with the very culture that had been used to immunize him. Crombie noted the occurrence of a case of typhoid fever in a physician who gave a positive Widal reaction fourteen days before he came down with the disease. A number of such observations have been noted by Ruediger and Hulbert, and by Trowbridge, Finckel and Barnard. To summarize again our conviction in this matter, we would state that relatively high protection may exist in an individual with or without agglutinins or antibodies in the circulating blood, and, conversely, the presence of antibodies in the circulating blood is no indication either of absolute protection, which probably never exists, or of the degree of protection against typhoid infection.

We shall have occasion at a later point to discuss the typhoidin test, which has already been described in connection with typhoid recovery, as it occurs in individuals that have been artificially immunized against typhoid fever. We believe this test to be of distinct value as indicating an actual resistance to typhoid infection, or at least, when negative, as showing a failure to react sufficiently to insure a normal degree of protection.

A further reaction following immunization, which again suggests the clinical picture of typhoid fever itself, is the enlargement of the spleen in some six per cent of the cases, that has been noted recently by Kammerer and Woltering, Frugoni, and Goldscheider.

CHAPTER XI

THE PROTECTIVE VALUE OF VACCINATION AGAINST TYPHOID FEVER

It took some eight years (1896–1904) for Wright and others to interest the world seriously in typhoid vaccination as a means of actually preventing typhoid fever, and some five years longer before the methods laid down by German and English investigators at the earlier date could be thoroughly tested out and approved in practice. Any matter of statistical proof of this sort requiring the actual treatment and subsequent observation of large bodies of men would of necessity require time, and, in common with all matters which affect so deeply the life and health of the individual and community, has met a wise and critical skepticism. Antityphoid inoculation has also, in common with all measures designed to protect the public health, been bitterly opposed by agitators who, when faced by a fancied infringement of personal rights, are blind to all calm inspection of evidence. The bulk of the statistics on which our final judgment must rest as to the remarkable efficacy of antityphoid vaccination, has been accumulated from the results of vaccination in armies. A large group of facts is now available and of thoroughly convincing nature, obtained not only from armies but also from institutions and among the civilian population, particularly when exposed to acute epidemics of the disease against which this method is designed to protect. The logical value of the proof that may be collected is extremely variable, as one might expect, depending not only on the accuracy of the observer, but also on the nature of the individual group experiments themselves. No statement derived from an indefinite clinical experience in administering the vaccine and observing failure or resistance from subsequent typhoid infection could, of course, be of any considerable value. We may classify, for the sake of comparing certain figures which we shall subsequently adduce, the types of evidence on which our conclusions in reference to typhoid vaccination have been based, listing them in the order of their relative importance.

We have, first of all, certain definitely controlled experiments in large numbers of soldiers in which comparison of the incidence of

disease has been noted in more or less equally divided groups of vaccinated and unvaccinated men in the same regiments, who are exposed to the same danger of infection. Such evidence is afforded, for example, by the results obtained in the British troops in India, where vaccination has been voluntary. We have, moreover, in the partial vaccination of the inmates of institutions still more rigidly controlled experimental conditions.

And, again, we have the accumulating evidence of a large body of men, as, for example, the United States Army, in which subsequent to a certain period vaccination has been compulsory. In this case a diminution in the morbidity and mortality rate from this disease may be compared with the previous incidence of the disease in the same body of men. This evidence is not quite so convincing, inasmuch as the fluctuation and incidence of typhoid fever is known to be considerable and the introduction of other hygienic measures in the way of detection of carriers and purification of water supply may to some minor extent have aided in the remarkable diminution of the disease that has been brought about. In other words, a lessened danger to infection may have accounted, at least in part, for the reduction in morbidity that has taken place.

Lastly, we have uncontrolled experiments, as among the civilian population, where conclusions are drawn by a number of different individuals, where the degree of exposure between vaccinated and unvaccinated must be extremely variable, and where the only conclusion of any significance would be a striking diminution in the total death rate of the vaccinated community. As we shall see, whereas a difference in morbidity and mortality rate from typhoid fever is of vital significance in comparing an army group of vaccinated and unvaccinated individuals, it is of little value under the conditions of civilian life. As a matter of fact, it will frequently be found that the vaccinated individuals in a general community suffer a higher morbidity rate from typhoid fever than the general morbidity rate of the state or district from which they come, owing to the fact that it is usually those individuals who recognize that they are most exposed to infection who become vaccinated.

We may proceed, then, to a consideration of the efficacy of typhoid vaccination by considering as impartially and as fully as possible what the actual result has been in the various groups of individuals that have been mentioned, beginning with the larger and controlled groups afforded by certain of the armies of the world. The armies and navies present not only controlled experiments but in most ways unusually standard hygienic conditions,

and to some extent uniform conditions of exposure. They further represent standard vaccines given in a more or less uniform manner and properly prepared and conserved.

THE ENGLISH ARMY

When we consider that the sun never sets on the British Empire, it will readily be understood that no body of men has ever been exposed to more varied and often to greater danger of typhoid fever than the English Army. It is fortunate, therefore, that an Englishman, Sir Almoth Wright, was the first to deal effectively with the problem of the control of this disease by means of vaccination. The varying conditions of exposure to typhoid to which the English Army has been subjected in various parts of the empire in peace times is evident from the following table compiled from statistics that have been furnished by Smith for the year 1898.

TABLE XV

MORBIDITY AND MORTALITY FIGURES FROM TYPHOID FEVER PER 100,000 OF ENGLISH TROOPS IN THE YEAR 1898 IN DIFFERENT LOCALITIES

Locality	*Morbidity*	*Mortality*
Great Britain	120	24
Gibraltar	420	132
South Africa	3290	577
India	3600	1000
Egypt	8100	2340

High as is the mortality in certain colonies of the British Empire, it was even more remarkable in certain localities of India, where, for example, in the Khyber district the morbidity of this year was 16,050 per 100,000 with a mortality of 4060. It is interesting, further, to compare the mortality rate in England for the general population during this same year, which was only seven.

These figures, shocking as they are, represent the relatively low mortality from this disease in peace times which, as we have already noted, is invariably increased during times of war. During the Boer War (1899–1902) in which 380,605 troops were engaged, the morbidity from enteric fever, which, to be sure, included paratyphoid as well as typhoid infections, in the English Army was 57,684 cases, or a morbidity per 100,000 of 15,115 with a mortality of 2100.

Between the years 1896 and 1904 Wright and his successors carried out over 100,000 inoculations in India and elsewhere. The distinctly favorable results of this labor are published in a series of

articles, and certain groups of them are tabulated in the following table, which is aimed to represent the best controlled and significant figures from the results of typhoid vaccination in the English Army at successive periods before the present world war.

TABLE XVI

RESULTS OF ANTITYPHOID IMMUNIZATION IN THE ENGLISH ARMY. MORBIDITY AND MORTALITY PER 100,000

Locality	*Vaccinated*			*Unvaccinated*			*Authority*
	No.	*Morbid.*	*Mortal.*	*No.*	*Morbid.*	*Mortal.*	
India 1900	10501	914	161	83135	1665	444	Wright [3]
India 1909	5473	380	36	6610	2830	390	Leishmann
India 1910	58481	260	29	10794	1390	220	Firth
Various colonies 1913	10378	539	40	8936	3040	500	Report of the Antityphoid Committee, London, 1913

The first results obtained by Wright, although encouraging and showing a diminution both in morbidity and mortality, which was about two-fold in the vaccinated as against the unvaccinated, are still far behind the subsequent results that have been obtained. And, as Wright himself was first to point out, certain objections could be raised against the method, as was evidenced by certain untoward results that occurred in a few army groups shortly after immunization. In certain regiments in India severe and even fatal cases of typhoid occurred in considerable numbers in vaccinated individuals, and even when they did not occur so frequently in unvaccinated men of the same troop. The exact reason for this occurrence is probably not quite clear, but certainly would not seem to be due to the existence of a "negative phase," to which Wright attributed these unfortunate accidents. At all events, the Medical Advisory Board suspended antityphoid inoculations in the English Army for some eighteen months, beginning 1903 (Bruce). Wright's procedure was later ratified by the College of Physicians (Harrison), and has since proved generally efficacious, as the later results in the table indicate. The cause of failure in the earlier results was due in all probability to the fact that a single inoculation was given instead of the two or three which have subsequently been required, and also to some extent to the fact that the vaccine was more or less inactive through having been heated to 60° as in the original procedure recommended by Wright. It was pointed out by Ward that the incidence of typhoid fever among those who

have received two injections of vaccine was distinctly less than among those who had received a single inoculation.

The later results, some of which are summarized in Table XVI, show that there has been a distinct improvement since Wright's original method was supplanted by the modifications of Leishmann, the most important of which consisted in requiring two doses of vaccine and killing the vaccine by heating to 53° and then adding phenol. Vaccination in the English Army has been and remains voluntary, although it was found by Firth that at the time of his report, 1910, in India, 82.3 per cent of the men had received the treatment, an increase in four years from 6.6 per cent. His figures, moreover, demonstrate that the morbidity rate between 1906 and 1910 in India fell gradually from 15.6 to 4.6 per cent, and the mortality from 3.19 to 0.63 per cent. The report of the English Antityphoid Commission published in 1913 deals with the most representative and best controlled units of the English Army in respect to vaccination in different parts of the empire and investigates carefully the incidence of 19,314 cases of the disease in respect to previous vaccination. Their conclusions, as evidenced in the table, may be stated in another way as showing that the morbidity in the vaccinated was only one-sixth of that in the unvaccinated, and the mortality one-ninth. Furthermore, only twenty-six of the fifty-six cases that occurred in the vaccinated were in individuals who had been fully vaccinated within two years. They recommend further investigation of the types of vaccine and universal compulsory inoculation.

The protective value of antityphoid vaccination has been fully justified in the results obtained in the British Army during the present world war. Whereas ultimate statistical results are impossible at this time, certain figures that have been made public are of extreme and convincing value. Vaccination is apparently not yet a matter of compulsion in the English Army, although it is estimated by Fleming that ninety per cent of the men have actually been inoculated. Three injections apparently are now being given (Vincent and Muratet) instead of the two that were the routine before the present war. Mr. Foster made the statement in the British House of Commons that there had been 1501 cases of typhoid fever in the British Army during the first two years of the war (to August 25, 1916). Of these, 993 cases occurred among vaccinated men and 508 among the uninoculated. If we are justified in estimating that ninety per cent of the total army had been vaccinated, it would mean that the vaccinated

were approximately five times as well protected as the unvaccinated.

THE FRENCH ARMY

Vaccination did not begin in the French Army until the year 1911, when it was tried out in certain garrisons in France and in Morocco and Algeria. Several different types of vaccine have been tried, but the one recommended by Vincent, a polyvalent vaccine, with the organisms killed by ether, and later improved by the addition of strains of paratyphoid bacilli, is the one now in general use. The regular number of injections at first were four, but following a special report before the Hygiene Committee in 1914, it was decided that owing to the exigencies of the war they could be reduced to two by increasing the size of the dose employed, for, as we have already stated, the actual amount of vaccine would seem to be more important than the number of injections. This shortened course, however, would not seem to have given as favorable results as in the smaller groups of cases in which four injections were given before vaccination became obligatory through the law passed the twenty-eighth of March, 1914 (the Leon Labbé law). The excellent results obtained in the earlier sets of inoculations are summarized in the following table.

TABLE XVII

RESULTS OF VACCINATION IN THE FRENCH ARMY BEFORE THE WORLD WAR. MORBIDITY AND MORTALITY PER 100,000

Locality	*Vaccinated*			*Non-Vaccinated*			*Authority*		
	No.	*Morb.*	*Mort.*	*No.*	*Morb.*	*Mort.*			
Avignon 1911	1366	0	0	687	22561	3202	Vincent and Muratet		
E. Morocco 1911	—	0	0	—	6497	835	"	"	"
Algeria 1912	—	9	0	—	1214	188	"	"	"
Tours 1914	1646	0	0	488	19900	4340	"	"	"

Particularly striking are the extraordinary results obtained in the epidemic which broke out in Avignon in 1911, which has been frequently quoted. It is probable, however, that it is more possible to avoid infection in epidemics like this in civilized surroundings than in a country like Morocco, where the sources of infection are not so evident.

In spite of the law requiring vaccination, it would appear from the somewhat indefinite statistics that have become available since the beginning of the present war that not all the soldiers have actually been vaccinated. Whereas Rist estimated in 1916

that 73.9 per cent of the army were vaccinated, certain German observers (Stursburg and Klose) found that only fifty-four per cent of 2782 French prisoners had been vaccinated and that typhoid was of relatively frequent occurrence among them, although its incidence was diminished markedly in those that had had four injections. It has been stated * that in the first year of the world war there were 1347 cases of typhoid of which 891 were among the uninoculated and 256 were among the inoculated. In the first group there were 155 deaths or 17.4 per cent mortality, whereas among the 256 inoculated there were only eight deaths, a mortality of 3.1 per cent. Vincent and Muratet state that re-vaccination is being practiced at yearly intervals, a single injection being given. Paratyphoid fever is, as we shall see, relatively frequent in the French armies, which we think must be attributed to a failure to have utilized the triple vaccine (typhoid, paratyphoid A and paratyphoid B) that Vincent recommended as a routine. There is evidence from some reports, for example Cade and Vaucher, that there must have been considerable irregularity in the number of injections given, and it appears evident that those that received the greater number are the better protected.

THE FRENCH NAVY

Vaccination against typhoid was voluntary in the French Navy to March, 1915 (Chantemesse [3]), and then became obligatory, four vaccinations being required. The numbers over a period from August 1, 1914 to April 1, 1916 of vaccinated and unvaccinated soldiers were approximately even, with about one-fifth as many cases among the vaccinated as among the unvaccinated, and only one-seventh the number of deaths.

THE RUSSIAN ARMY

According to Tarassevitch, typhoid vaccination has been obligatory in the Russian Army since August, 1915. The vaccines are prepared in various bacteriological institutes and sent to five control laboratories in the larger cities, where they are studied and tested for their absence from untoward effects. The vaccines are similar to those employed at the Pasteur Institute. No results are as yet available as to their efficacy.

* Editorial, J. State Med., Feb., 1916, Vol. 24.

THE ITALIAN ARMY

Triple vaccines were employed in 1912 and 1913 in Cyrene, Tripolis, and finally in Italy (Vincent and Muratet). In the earlier part of the work Pfeiffer-Kolle vaccines were used interchangeably with Vincent's vaccine, but in Northern Africa it became evident that Vincent's vaccine affords far better protection, as is evidenced from the following table which we borrow from Vincent and Muratet (Table XVIII). In small groups of individuals, since Vincent's vaccines have been employed, very good results have been obtained.

TABLE XVIII

MORBIDITY FROM TYPHOID PER 100,000 VACCINATED IN THE ITALIAN ARMY IN AFRICA

Vaccine Employed	*No. of Injections*		
	1	*2*	*3*
Vincent's triple vaccine	440	270	30
Pfeiffer-Kolle vaccine	1070	690	720

THE JAPANESE ARMY AND NAVY

The incidence of typhoid fever in the Japanese Army before and after the introduction of vaccination has been summarized by Yagisawa. Whereas during the Russian and Chinese wars (1897–1903) the incidence averaged five hundred per 100,000 with a mortality of one hundred, and later rose to eight hundred with a mortality of one hundred and thirty, in 1908 with the introduction of vaccination (A. Netter) the morbidity dropped to seventy and the mortality to eight. There were approximately one-tenth as many cases in the vaccinated as in the non-vaccinated (Chantemesse [4]).

In the Japanese Navy typhoid fever increased from 1902 to 1907 until it had reached 920 cases per 100,000. From 1908 to 1911 varying numbers of individuals were immunized, first against typhoid, about sixty-three per cent, and later against paratyphoid A (forty-two per cent), and paratyphoid B (twenty-seven per cent). The disease steadily decreased during this period until the incidence of the three diseases reached the following figures per 100,000 in the vaccinated and unvaccinated (Kabeshima).

TABLE XIX

CASES OF THE TYPHOIDAL FEVERS IN VACCINATED AND UNVACCINATED MEN OF THE JAPANESE NAVY

	Typhoid	*Paratyphoid A*	*Paratyphoid B*
Vaccinated	24	38	0
Non- "	186	87	140

THE GERMAN ARMY

The general morbidity figures in Germany have been extremely low, reaching in 1912 something like three to the 100,000, and in Prussia, 1909 to 1910, eight to the 100,000, owing largely to the introduction of proper sanitation and the elimination of carriers (Kossel).

The German Army has been relatively backward in adopting typhoid vaccination, particularly in view of the fact that the early scientific experiments on which the present methods are founded are due to Pfeiffer and Kolle. Vaccination, indeed, was not taken up seriously until the war against the Herreros (1904 to 1907), when the Government appointed a committee consisting of Koch, Gaffky, Kirschner, Donitz and Kolle to investigate its advisability. In the troops in Southwest Africa during the Herreros rebellion vaccination as recommended by this Commission was found to give distinct though only moderately successful results, as compared with results that were already being obtained elsewhere. Kuhn reports that in 7287 soldiers that were vaccinated the incidence was at the rate of 5100 per 100,000, with a mortality of 330, whereas in 9209 non-vaccinated it was nearly twice as large, 9900 per 100,000, with a mortality of 1260. It is further noted that the disease was much milder in the vaccinated and that the incidence varied distinctly with the number of injections that had been given. It is quite probable that the failure to obtain better results in these earlier campaigns was owing to the employment of the Pfeiffer-Kolle vaccine, which has since been shown in other hands to be of less immunizing value than other vaccines. The results in the present great war are largely a matter of guess work, although there is evidence that several different vaccines have been employed. For example, Goldscheider and Kroner speak of vaccination of the troops in 1914 with the Marx vaccine, whereas Sachs refers to the use of Kolle and Pfeiffer vaccine as a routine, with three injections.

Considerable skepticism has been expressed in Germany during the present war as to the actual protective value of typhoid vac-

cination (see, for example, Scholz and Hirsch), which seems extraordinary in view of the general acceptance of the method elsewhere. At all events, a considerable number of cases of the disease in the vaccinated have been reported (Mayer [2] and Bujioid).

THE UNITED STATES ARMY

The results obtained by typhoid vaccination in the United States Army have been widely and justifiably famous. The splendid results that have been achieved are attributable to the initiative of Major Russell, who, after the study of the conditions of antityphoid vaccination in England, introduced and was able to have compulsory vaccination enforced in July, 1911. Voluntary inoculation, as is shown by the accompanying table, was followed by a decrease in the number of cases, and compulsory vaccination by the almost complete disappearance of the disease. The results of the United States Army evidence not only the value of vaccination in itself, but the value of having a body of men that is completely vaccinated. Typhoid fever has not, however, absolutely disappeared even in the completely vaccinated troops, but vaccination has reached a maximum of efficiency, which is astonishing.

TABLE XX

THE DECREASE OF TYPHOID FEVER IN THE U. S. ARMY FOLLOWING THE INTRODUCTION OF VACCINATION. (RUSSELL AND LYSTER)

		Cases per 100,000	*No. Vaccinated*	*Army Strength*
1901	No vaccination	674		
1902	" "	699		
1903	" "	514		
1904	" "	435		
1905	" "	314		
1906	" "	572		
1907	" "	379		
1908	" "	320		74,692
1909	Voluntary	335	830	—
1910	"	243	16,093	81,434
1911	½ compulsory	85	25,779	82,802
1912	Compulsory	31	all	88,478
1913	"	4.4	"	90,752
1914	"	7.5	"	92,877

Eight cases of typhoid appeared in the army in 1915, four of which were in Hawaii, according to the Report of the Surgeon General, and it is evident from current reports that they are still

occurring in the regular army.* The added danger of infection under conditions of actual warfare is suggested by the increase in number of cases during the summer of 1916, when large numbers of troops were concentrated on the Mexican border. Chamberlin reports that twenty-four cases occurred in regular and militia troops between May 1 and October 18 of this year.

THE UNITED STATES NAVY

The United States Navy employs the United States Army vaccine, its use being obligatory in all enlisted men under forty-five years of age, with re-inoculation on every re-enlistment, that is to say, every four years. Since the introduction of vaccination the number of cases has dropped from an annual average in 1909–1911 of about two hundred to seventeen (1913–1915), according to the Annual Report of the Surgeon General, U. S. Navy, 1916. The few cases that have occurred in these later years have been almost entirely in those who had been vaccinated three or four years previously, and a shortening of the period before re-inoculation is under consideration.

A certain number of failures in vaccination should be anticipated in view of individual variations in reaction, and in the advent of greater exposure these failures are almost certain to increase. The method of vaccination in the American Army is practically the same as that employed in English troops, and has been carried out with an old English stock strain (Rawling's) obtained from Leishmann. The only innovation introduced was the addition of a third dose of vaccine which has since been adopted by other nations. One of the most important reasons for the remarkable success obtained in this large group of men over several years is undoubtedly due to the fact that they have constituted the first completely vaccinated aggregations, the importance of which fact has already been referred to.

A careful consideration of the results in the armies of the world which have to any extent employed typhoid vaccination shows conclusively the remarkable, and at times, wellnigh perfect protective value of the method. The results, moreover, demonstrate as in the British Army where vaccination has been carried out for the longest period, that distinct improvements have been made in the method of vaccination, some of the reasons for which are clearly evident, as for example the adaptation of a method of killing the vaccine at lower temperatures and increasing the number or size of

* See Military Surgeon, Feb. 1917, p. 240.

the doses. Any comparison between the results obtained in one army with another is more difficult. It seems suggested at least that, apart from improvements in the killing of vaccines and dosage polyvalency, sensitization and other variations may affect the efficiency even more markedly. We have, for example, the observations of Ciuca, Combiescu and Balleanu, where it was found that Besredka's sensitized vaccine protected troops better than the Pfeiffer-Kolle vaccine. A similar tentative conclusion may be drawn from certain observations quoted by Vincent and Muratet that were obtained in the Italian Army,* where the morbidity rate in certain North African troops was shown after three injections of the Pfeiffer-Kolle vaccine to be 7.2 per 1000, whereas it was only three-tenths per 1000 when the same amount of Vincent's vaccine was used.

We have already mentioned that the tendency has been to increase the number or size of the doses of vaccine employed. This increase in dosage has depended largely on army observation, and particularly on the relatively greater number of failures of typhoid vaccination with the small than with the large doses. Thus Goldscheider and Kroner found that of three hundred cases of typhoid among the vaccinated one hundred and twenty-five had had only one or two inoculations, whereas only thirty-nine occurred in the preponderating group that had received three injections. Similar results have been noted by Leger, Abt and Dumont and by Labbé.

A matter of considerable importance in the success of vaccinating armies depends, we believe, on the inclusiveness of the vaccination that has been obtained. It has already been suggested by Sawyer [4] that the unusually successful results in the United States Army may have been due to some extent to the fact that the entire body of men was vaccinated. As corroborative of this point, we may mention that Widal [4] has shown that in certain groups of the French troops, where typhoid had been practically obliterated, it reappeared in spite of continued vaccination when fresh unvaccinated individuals were added to them at the beginning of the present war. It is further evidenced from the figures of Fleming that, as the English forces became more fully inoculated, the number of cases of typhoid among the inoculated decreased as well as the actual number among the uninoculated, although, of course, the difference between the two was at all times very evident. Sergent and Negre find the incidence of typhoid among the few unvaccinated in the army remains low, al-

* See p. 179.

though relatively high among the adjacent civil population which is largely unvaccinated. In other words, the elimination of all foci of re-infection would, of course, tend to diminish the danger of exposure, which may result in typhoid even in the vaccinated.

ANTITYPHOID VACCINATION IN INSTITUTIONS

Vaccination against typhoid fever in insane hospitals and prisons has been very successful. This success again proves the efficacy of the method itself, because in institutions we have perhaps the most ideally controlled experiments available. Not only are some vaccinated and some left unvaccinated as controls, but those that are vaccinated are inoculated in a uniform manner, and both groups are subjected to almost identical dangers of contagion in so far as fixed residence can contribute to such stability. Among the successful results may be mentioned those reported by Hatchel and Stoner,[2] who found that in the institutions of Maryland, of 5512 individuals that had been vaccinated only three subsequently suffered from typhoid fever, a morbidity rate of fifty-eight to the hundred thousand, whereas the rates in previous years had been from five hundred to two thousand per 100,000. In the asylum at Braqueville Besredka reports that in 516 vaccinated individuals no case of typhoid appeared, whereas in 434 unvaccinated four cases occurred during the same period. The results, however, are by no means as uniformly successful as those that have been quoted. Wade and McDaniel, for instance, in Minnesota found that in an asylum where carriers were subsequently proved to exist there were a considerable number of cases among the vaccinated as well as the unvaccinated, in spite of a positive Widal in the former, and they wisely suggest that vaccination alone is not sufficient to obliterate typhoid fever and that the protection following vaccination must to some extent depend on the degree of exposure.

VACCINATION AMONG PHYSICIANS AND NURSES

Nurses and physicians probably undergo the maximum degree of exposure to typhoid infection. It has been estimated by Richardson and Spooner that they are eight times as liable to the disease as the ordinary individual. Spooner has reported his results with 1585 vaccinated nurses in Massachusetts with a morbidity rate of 150 per 100,000, whereas in 674 uninoculated in the same institutions the morbidity rate was 1190 per 100,000.

Ogan has, on the other hand, reported a number of failures of vaccination among nurses and physicians exposed to a carrier. Some of the failures may have been due to the type of vaccine employed. Townsend found in Waterbury, Connecticut, that among eighty vaccinated nurses there were no cases of typhoid in a given epidemic, whereas four occurred among thirty-five unvaccinated. Elmer, again, cites instances in which practically the same number of cases occurred among the vaccinated as among the unvaccinated. In all matters of this sort where the results are found to vary, the more successful ones may be taken as indicative of what may be hoped for under milder conditions of infection or best conditions of vaccination, and the failures in certain instances are no reason for losing faith in the method.

VACCINATION AMONG LABORATORY WORKERS

Kisskalt has analyzed fifty cases of laboratory infection of typhoid fever, seven of which were in vaccinated individuals. Laboratory infections represent by all odds the most massive type of infection, as they are usually caused by swallowing cultures of the living microorganisms, which must represent relatively enormous infecting doses. Kisskalt would attempt to explain away failures of this sort on the basis of incomplete vaccination, weakness of the vaccine, and the like. It would seem to us much more reasonable to admit them frankly as failures of a method which could never be expected to be absolute and the success of which must depend on the usual hygienic observances, and again on the degree of infection that is undergone. We have already cited the instances of Marx and of Crombie, and may mention in addition the one of Auché and Chevaillier, which show clearly that typhoid may occur in completely vaccinated persons.

RESULTS OF TYPHOID VACCINATION IN CIVIL COMMUNITIES

Typhoid fever is not only a community but an individual problem, and the individual is therefore concerned in the benefit of typhoid vaccination as much as the group. The individual is, however, exposed to certain dangers of infection and protected from certain other dangers which may occur in armies or in institutions. The severest trial of typhoid vaccination will for many years be among the general population, and failures will continue to occur among the vaccinated, and only in decreasing frequency with the increasing percentage of a community that is vaccinated.

If the people would hasten the ultimate obliteration of the disease, they might do so by being vaccinated, not when threatened with an unusual exposure to typhoid fever, but under the ordinary conditions of existence in which one is relatively protected in modern civilized communities. In spite of the occurrence of typhoid in the vaccinated, which, as we have stated, in general communities may actually exceed the normal rate, owing to the greater exposure, there are very well defined instances of striking beneficial effect produced in small communities by this means. For example, Vincent [10] reports the results in the town of Paimpol, where four hundred individuals when threatened by an epidemic were vaccinated and subsequently developed no cases of typhoid, whereas two cases occurred in two unvaccinated families. Spooner reports equally interesting results in Greensboro, where sixty-five people were markedly exposed and seventeen had already suffered from the disease, and where of twenty-nine vaccinated individuals only one came down with the disease, whereas among nineteen uninoculated five cases developed. The results of Hatchell and Stoner in the general population, when compared with the success they obtained with physicians and nurses and in institutions, bring out conclusively the results that may be expected in general life. They have records of 7714 in the general population with a morbidity rate of 77.5, which, of course, markedly exceeds the rate for the state. A similar slight increase over the state morbidity rate has been shown by Sawyer in his comparison of different types of typhoid vaccine in California. His figures would indicate a distinct advantage in the protective value of the Gay-Claypole sensitized vaccine sediment over commercial typhoid vaccines of the army type. Other instances of failure of typhoid vaccination in individual cases in civil communities have been noted by Gaither and many others.

Estimation of the actual protective value will in this group of cases remain difficult, since, first of all, their number is indefinite, the methods of vaccination extremely variable, both in technique and in vaccine employed, and, finally, there is no strict control of the incidence in unvaccinated individuals under anything approaching similar conditions of exposure.

TYPHOID FEVER IN THE VACCINATED

Much information has been gained concerning typhoid vaccination, not alone from its successes but also from its failures. Of these, there have been a plenty during the great world war,

and although it is impossible to consider them statistically in their entirety, the numerous facts that have already emerged are not only themselves of interest but will lead to a further understanding of typhoid vaccination and to means of increasing its efficiency. Failures following typhoid vaccination may in many instances be explained by errors in the administration itself, by too few vaccinations, or by improper vaccine, or, again, by the recent date of the vaccination, which must have antedated infection a sufficient number of days to ensure the maximum protection that may be afforded. But there are a sufficient number of instances of real failures, where the individual has been vaccinated at a properly antecedent date, where the full course in injections which is shown to produce protection in the majority has been given, and even where the presence of antibodies in the circulating blood has been demonstrated. As a concrete illustration of true failures may be noted the cases of a physician described by Hueppe,[2] who in spite of three full courses of inoculations fell ill of typhoid fever. These true failures again illustrate the relativity of any method of this sort, a conception fundamental to its full understanding.

With the increase in the number of failures, which has occurred under the unusual opportunities for infection that have occurred in the great war, has come much information as to the underlying causes, and the failures should in no way bring a sense of discouragement with the method itself. We find that not only is antityphoid vaccination relatively protective, but that the failures themselves are relative and not absolute. Thus, it has been shown * that although the morbidity rate of typhoid fever in the French troops has actually risen from 1.88 per 1000 in 1911 to 4.40 per 1000 in 1915, the mortality rate from this disease has fallen at the same periods from 0.27 to 0.15. It should further be pointed out that under the heading of typhoid fever in such statistics are unquestionably included those cases of paratyphoid which, as we shall presently discuss, have in no way been abated by antityphoid vaccination, and have actually increased, as might be expected, owing to the greater danger of infection afforded in active service. These figures simply illustrate a truth, which has become more and more evident since the statistics of antityphoid vaccination have accumulated, that the mortality among the vaccinated, as compared with the unvaccinated, decreases even more markedly than the morbidity, and it is, of course, with these ultimate results that we are more concerned. We have already given illustra-

* Editorial, Presse Méd., Feb. 17, 1916.

tions of this relative reduction of mortality over morbidity, but a number of instances from the present war may be of interest, not only as bearing on the total morbidity and mortality rates from typhoid, but on the respective rates in the vaccinated and unvaccinated. Bech found a mortality of sixteen per cent in his unvaccinated typhoid cases, whereas the rate in the vaccinated was 2.7 per cent. Bernard and Paraf had a mortality of 24.3 in the unvaccinated and 5.3 in the vaccinated. Donaldson and Clark had a mortality of fifteen per cent in the unvaccinated and of zero in the vaccinated. These figures taken from three of the greatest armies involved in the present war show very clearly the beneficial effects of typhoid vaccination even in those cases that from one aspect may be regarded as failures of the method.

Not only is the mortality rate decreased in vaccinated individuals, who in spite of vaccination become infected with typhoid fever, but the disease itself is found to undergo a very distinct modification when it does occur in the vaccinated. It has frequently been found to be so mild as to offer great difficulty in its classification. Thus, Schläger has observed a mild type of fever in six per cent of his vaccinated men when they were exposed to infection, which he regards as typhoid in all probability. Bernard speaks of "l'embarras gastrique febrile," a typhoidal infection among the vaccinated, and Hirsch,[2] Frugoni, Goldscheider and Kroner, Meyer, Lampe, Olmer and many others speak of the extreme mildness of typhoid that may occur in spite of vaccination. Sartori, Spillmann and Lasseur find that the disease in the vaccinated usually runs only ten to fifteen days. Goldscheider and Kroner note that the fastigium is either very brief or does not occur at all, the fever beginning in an abrupt manner and frequently aborting. Correlative with these findings are the observations of Hohlweg, Labbé and Lampe that typhoid bacilli are found with less frequency in the circulating blood in the vaccinated. Fewer complications are usually noted in the vaccinated, although it would seem that relapses are as frequent as in the unvaccinated (Hirsch,[2] Goldscheider and Kroner).

We may, if we like, consider these failures of typhoid vaccination as suggesting the value of a polyvalent vaccine, for they have been attributed with a certain degree of circumstantial evidence by Vincent and Muratet to infection with an unaccustomed race of bacilli.

Diagnosis of typhoid fever in the vaccinated is difficult, not only from the mildness of the symptoms which characterize it, but also from the fact that previous vaccination renders the ordinary

method of diagnosis by agglutination tests difficult or impossible. We have already discussed the usual occurrence of agglutinins following typhoid immunization and have further shown that the presence of a positive Widal is no insurance against infection with the typhoid bacillus. Such a positive reaction in cases of infection, however, renders diagnosis difficult. Among the methods suggested for diagnosis of typhoid fever in the vaccinated by agglutination tests is the observation of a rising agglutinin titer on successive days in the suspected febrile individual (Seiffert; Aldershof; Hirsch [2]). A constantly negative Widal, on the other hand, according to Courmont, Chattot and Pierret, tends strongly to rule out typhoid fever in a vaccinated individual. The assertion by Tidy that paratyphoid fever will cause the typhoid agglutinins to disappear has been amply disproved by the more extensive observations of Dreyer, Gibson and Walker.[2] According to Garbat,[2] a positive fixation reaction indicates typhoid fever rather than vaccination. Co-agglutination of Bacillus enteritidis is said to be present in typhoid fever but not in vaccinated individuals. The most certain method of diagnosis of typhoid fever, the isolation of the typhoid bacillus from the blood, is doubly valuable in detecting typhoid in the vaccinated.

PARATYPHOID FEVER IN TYPHOID VACCINATED INDIVIDUALS

The frequent occurrence of typhoidal fevers in vaccinated individuals during the present world war temporarily, and in the absence of careful laboratory examination, was the cause of some discouragement as to the efficacy of typhoid vaccination. It has since, however, been found that the majority of such fevers are not true typhoid fevers due to the bacillus of Klebs and Eberth, but are caused in the majority of instances by one of the paratyphoid bacilli, or in another group of cases apparently by a type of coccus. We shall later consider the paratyphoid fevers, the importance of which has become more thoroughly appreciated by these observations, in more detail and confine our attention at this point simply to the existence and occurrence of paratyphoid infections among those who have been vaccinated against typhoid.

It seems definitely proven that under usual conditions typhoid fever is of more frequent occurrence than the paratyphoid fevers, not only in general communities, but in armies under the extreme conditions of exposure during war (Chantemesse). One of the most striking facts brought out by the observations in the present war has been that typhoid vaccination has little or no effect in

preventing paratyphoid fever. This fact has been noted and agreed to by practically all the observers in the various armies (for example, Dreyer, Walker and Gibson, and Deve). It has been suggested, however, by Bernard,[2] and corroborated by Labbé that typhoid vaccination may lower the mortality in paratyphoid fever, although it does not diminish its incidence. Labbé, for instance, finds that the mortality from paratyphoid in a series of 800 cases among those unvaccinated against typhoid was 11.5 per cent, whereas among the typhoid vaccinated it was reduced to 6.58 per cent. The frequent occurrence of paratyphoid in the typhoid vaccinated must have seriously affected and tended to increase the apparent failures in previous years, when diagnosis was based on purely clinical symptoms unsupported by blood cultures. The present war has shown very clearly that the ratio of typhoid to paratyphoid infections has been completely reversed as a result of typhoid vaccination. This has been shown to be true by the studies of Labbé and of Bauer, Abrami and Stevestre, Rist and many others. Bernard and Paraf,[2] for instance, have shown in a series of typhoidal cases in which careful blood cultures were taken that typhoid bacilli were isolated from thirty-two unvaccinated cases, and paratyphoid bacilli from twenty-six similarly unprotected individuals. In typhoid vaccinated individuals in the same series, however, typhoid bacilli were found in only forty-five cases, whereas paratyphoid bacilli were found in 222. In a similar way Bech found that a series of 1521 blood cultures gave forty-seven per cent of positive results. Of these positive results, Bacillus typhosus was found to account for forty-four per cent of the infections in the non-vaccinated, but for only fourteen per cent of the infections in the vaccinated, whereas paratyphoid bacilli occurred in only seven per cent of the unvaccinated and in thirty-one per cent of the typhoid vaccinated. The evidence, however, distinctly is that there has been no absolute increase but rather a decrease of the typhoidal fevers, owing to typhoid vaccination. In other words, the paratyphoidal fevers have increased relatively but not absolutely, and the total result would be a diminution of the entire group. Paratyphoid fevers were also a matter of considerable importance in the mobilization of the United States army on the Mexican border in 1916. Chamberlin states that there were 250 cases of this disease between May 1 and October 7, 1916, the majority of which were due to Bacillus paratyphosus alpha. The evidence is that in Europe, both the alpha and beta types have been present, the preponderance of one over the other varying with time and place; before the world war the

infections reported were mostly of the beta type, but during the war both forms have been present.

MULTIPLE VACCINATION

The diminution of typhoid fever, then, as a result of vaccination has led to disclosing and rendering more important the paratyphoid fevers. The paratyphoid fevers probably have always existed in equal numbers, but their importance has not been appreciated owing to a failure to differentiate them by laboratory methods from the typhoid fevers, and also owing to the former preponderance of true typhoid fever. It was suggested by Castellani in 1905 (Widal [4]) that vaccination, particularly of troops, to be most effective should consist in immunization not only against typhoid fever but against the paratyphoid fevers by the use of a triple vaccine compounded of the three specific organisms. The results in the present war have led to a warm support of this suggestion by practically all observers (Landouzy; [2] Dreyer, Walker and Gibson; [3] Leger, Abt and Dumont). Leishmann is practically the only one who has not been enthusiastic about the use of triple vaccine, owing to the fact that he has not regarded the number of cases as sufficient or the seriousness of the disease great enough to warrant this additional vaccination. There would appear to be no contraindication to such a measure on the ground of vaccination symptoms. A triple vaccine containing in all actually more bacteria apparently produces no more severe reactions than does the simple typhoid vaccine, according to the results of Kabeshima, Dreyer, Walker and Gibson; [3] Widal and Courmont; and Widal.[5] The usual dosage that has been recommended for such a triple vaccine has been 500 million typhoid bacilli and 250 million each of the two paratyphoid organisms. Widal [6] suggests employing equal amounts, and in collaboration with Salimbeni has found that a relatively large dose of mixed vaccine may be given in two doses, which together include ten billion bacteria, without serious effects.

It has been shown by several observers, notably by Widal and Sicard, by Castellani,[3, 5] and by Kabeshima, that injection of a triple vaccine of typhoid and paratyphoid bacilli will give rise to antibodies active against each of the organisms in question, and each one quite as strong as if a single organism had been employed. The first results from the use of this triple vaccine are probably those reported by Kabeshima, who states that the method has been in use in the Japanese navy since 1908 and that

striking diminution of all three of the diseases has been produced by this means. Reference has already been made to his report on page 179. Castellani recommended the method in 1905 and has reported on results extending as far back as 1909.[6, 8] Vincent[6] also was one of the first to recommend the use of a triple typhoid-paratyphoid vaccine, and at his suggestion the method was utilized in the Italian army in 1912 and in the French armies in Morocco in 1913 and 1914, with extraordinary good results. It may, then, be taken as a foregone conclusion that the use of paratyphoid vaccine, administered simultaneously with typhoid vaccine, will eventually lead to the decrease and disappearance of paratyphoid fever as well as of typhoid fever. Davison states that the use of a triple vaccine has been made compulsory in the British army since January, 1916.

Multiple vaccines of other sorts have been suggested, and to some extent employed in troops and individuals who might be exposed to several infections, particularly in the tropics. Thus, Castellani[9] has employed a vaccine containing not only typhoid and paratyphoid bacilli, but also plague bacilli and the spirilla of Asiatic cholera. Another vaccine which he has recommended includes the causative organisms of Malta fever and of dysentery. The use of different combinations of this type would, of course, depend upon the existing diseases in the locality in which the inoculated individual lives. Johnson and Milne have utilized a typhoid vaccine with the addition of dysentery bacilli, but find that the latter organisms must be sensitized in order to diminish the severity of reactions which they would otherwise cause.

DURATION OF THE PROTECTION AFFORDED BY ANTITYPHOID VACCINATION

One of the most important questions to be considered in any systematic attempt to apply typhoid vaccination is the duration of protection that may be expected from any given method employed. Estimates of this duration have rested largely on the accumulation of statistical evidence as to the tendency of failures to occur after a certain lapse of time following inoculation. Firth, to whom we owe the most careful statistics of this sort, estimated that the protection following the type of inoculation carried out in the British army in India tended to disappear rather sharply after thirty months. In other words, the duration of immunity might be assumed in the majority of troops treated in this manner to last some two and one-half years. These figures,

although representing an accurate mean for the group, give little information as to the duration of protection assured in the individual case. The duration would differ, moreover, in accordance with the method of inoculation employed, since some methods are recognized to afford longer protection than others. Castellani [1] thinks that the ordinary methods of typhoid immunization may be expected to last for one or two years. Kossel also estimates that typhoid immunity lasts from one to two years. Others have suggested that protection may last for five years or more.* In the United States army and navy it has been assumed that re-vaccination would be required only once in four years. In the French army Vincent has recommended re-vaccination every year. It is evident, then, from these figures that we have no accepted standard by which we may judge when re-vaccination is indicated on the average and when it should be applied in large groups of men. Of still greater importance is the question of individual protection, for we recognize from the failures that may occur at any period subsequent to typhoid vaccination, even in a few weeks, that certain individuals fail to respond sufficiently to be protected against the ordinary chance of infection.

Statistics are of no avail in assuring anyone that he or she is not protected against typhoid fever as the result of a previous vaccination, or should not be re-vaccinated in order to give greater assurance. We have already discussed in detail the inadequacy of estimating the agglutinin titer either in animals or in human beings as a measure of resistance against infection by the typhoid bacillus. We have seen on the one hand that those individuals best protected against typhoid infection, the typhoid recoveries, usually soon give a negative Widal test, and that men and animals with lower agglutinin titer, as for example after the use of sensitized vaccines, are often better protected than those with a higher titer. On the other hand, we have noted that the majority of typhoid vaccinated individuals show a positive Widal, which is usually higher than the ordinary typhoid recovery (Dryer, Gibson and Walker [3]), and yet such individuals are by no means invariably protected against typhoid fever, and individuals that gave a positive Widal a few days before infection have been described. We cannot, then, rely upon the determination of antibodies as usually estimated for indication as to the degree or the duration of protection afforded by antityphoid vaccination.

In an effort to devise a reaction of significance as indicating

* Editorial, Jour. Am. Med. Asso., July 22, 1916, p. 285.

resistance against typhoid fever, Gay and Force were led to develop the typhoidin test, the results with which have already been described in individuals that have recovered from typhoid fever. We have already mentioned that this test of localized hypersusceptibility to products of the typhoid bacillus has been acceptably proven to be positive in the majority of cases of recovered typhoid fever and negative in the majority of normal individuals.

The typhoidin test in vaccinated individuals has been found in the hands of Gay and Force, Gay and Claypole,[3] Mehler, Pulay, Force and Stevens, and Gay and Lamb to be for the most part positive, the percentage of positive reactions, in general, diminishing directly with the duration of the time that has elapsed since vaccination. In other words, they diminish with the known conditions which tend to the disappearance of resistance. There are a number of other facts which have led us to regard the typhoidin test with increasing confidence as an indication of immunity from typhoid fever. In the first place, the typhoidin reaction not only occurs in a higher percentage of typhoid recoveries than in typhoid vaccinated, but usually occurs with greater intensity in the first than in the second category (Pulay, Force and Stevens). The typhoidin test, although negative in normals will become positive in those same individuals after a course of antityphoid injections (Force and Stevens). On the re-vaccination of people who give a positive typhoidin test, the reaction to the typhoid vaccine is more marked, as is also the case in typhoid recoveries. The typhoidin test does not occur immediately after the termination of a series of inoculations, nor does it occur usually during the course of typhoid fever. In other words, it tends to occur when a condition of relative resistance has been established. The typhoidin test is frequently not found positive until a month after the end of treatment, which corresponds to the greater percentages of failures of typhoid vaccination immediately following inoculation.

A certain number of individuals even after the completion of the usual course of prophylactic inoculations give repeated negative typhoidin tests. This, we believe, may be correlated with the cases of failure which may occur even at the time when immunity is usually strongest. Of further suggestive value is the fact that typhoid fever has occurred in our experience in three vaccinated individuals in whom the typhoidin test was negative or doubtful, whereas infection has never so far occurred in the very considerable number of cases in which we have found the reaction positive.

As further indicating the prognostic value of the test, is the fact that a subsequent injection of typhoid vaccine will usually cause such a negative individual to give a positive test, thus agreeing again with the greater protection recognized to be afforded by a larger number or larger total amounts of vaccine.

One of the most interesting facts is the relation of the percentages of negative typhoidin tests, which occur at successive periods subsequent to vaccination, to the condition found on re-vaccination against small-pox.* A successful re-vaccination in small-pox, of course, indicates that the immunity of the individual has run out, in other words, that that individual is not protected against small-pox, and a successful re-vaccination, therefore, would correspond to a negative typhoidin test, if we may assume that both are indications of lack of resistance to the respective diseases in question. In the following table are shown, first of all, the increasing percentage of negative typhoidin tests which occur in successive years following antityphoid inoculation, and in parallel columns are listed the corresponding successful small-pox re-vaccinations obtained by Kitasato and Lescohier. The parallelism is certainly too striking to be accidental, and would unquestionably indicate a similar condition in the two instances, and furthermore tend to prove that the typhoidin test is really a measure of the degree of immunity to typhoid fever, whether acquired by recovery from the disease or by artificial immunization against it.

TABLE XXI

RELATIONS OF PREVIOUS TYPHOID VACCINATION, ON THE ONE HAND, TO THE PERCENTAGE OF SUBSEQUENT NEGATIVE TYPHOIDIN TESTS (FORCE AND STEVENS; GAY AND LAMB), AND, ON THE OTHER, OF PREVIOUS SMALL-POX VACCINATION TO SUCCESSFUL RE-VACCINATION (KITASATO; LESCOHIER)

Time Since Vaccination	*Typhoidin Negative*		*Small-pox Re-vaccination Positive*	
	F. & S.	*G. & L.*	*K.*	*L.*
1 year	27	36	14	28
2 years	45	36	33	33
3 "	50	46	47	58

For greater emphasis it may be re-stated that the object of this test as proposed by Gay and Force was not a method of insurance against infection with the typhoid bacillus, which certainly could never be given, not even following recovery from typhoid fever, but as an indication of a lack of resistance, which is quite another

* I am indebted to Dr. J. N. Force for calling this matter to my attention.

thing, and which serves a useful purpose in designating the particular individual that at any given time may require re-vaccination. In the voluntary immunization of students at the University of California it has been customary to request return a month after vaccination for a typhoidin test. If the test is negative, one or more further injections of vaccine are given. They are then urged to return at least every two years for a subsequent test, which when negative is taken to indicate need of another course of injections.

A further word may be said in reference to non-specificity in the typhoidin test. Nichols has found that some sixty-six per cent of the seventy-five per cent of typhoid vaccinated in his experience that gave a positive typhoidin test would also give a positive test to paratyphoidin alpha, and he very correctly remarks that recovery from typhoid or vaccination against typhoid affords no protection against paratyphoid. It is questionable whether Nichols' results would have been obtained if he had followed the forty-eight hour observation which we have since found to be more correct, and if he had used the intradermal method of testing. We ourselves have found in a certain number of cases that typhoid recoveries gave positive paratyphoidin reactions by the earlier cutaneous test, but almost invariably much less marked reactions to paratyphoidin than to typhoidin, the single exceptions being cases of authenticated paratyphoid fever. In other words, it is probable that a quantitative difference in the paratyphoidin reactions in typhoid recoveries could readily be demonstrated. But, even supposing these group reactions to be present, such results could not be taken as invalidating either the fact that a positive typhoidin test is an indication of relative protection, and certainly not as invalidating the only conclusion on which we wish to insist, that a negative test is an indication for re-vaccination.

One point remains to be mentioned before terminating our discussion of antityphoid immunization: that is, whether or not vaccination is to be recommended as a procedure during the incubation period of the disease, as when an individual is actually known to have undergone or been exposed to infection. Authorities apparently differ markedly on this subject. Thus, Hirsch [2] and Cammaert regard vaccination in the incubation period as leading to a negative phase and increasing the incidence of severe cases. The majority of observers, however, would either attribute no effect to such vaccination, as, for example, Elmer, or would regard it of very distinct benefit, as do Chantemesse, Vincent,[7] and

Davis. Haibe, Vincent,[8] and Noack cite cases in which vaccination was promptly begun, following known laboratory infection with no resulting symptoms of disease. They are not, however, we believe, justified, owing to the absence of proper controls, in regarding the treatment in these cases as having actually prevented the disease.

CHAPTER XII

THE PARATYPHOIDAL INFECTIONS

There exists a group of human maladies closely allied to typhoid fever both in their clinical manifestations and in their respective causative agents. These paratyphoidal infections, as they are called, present themselves in each and all of the forms of disease in which typhoid fever occurs, although with different relative frequency. We find localized infections such as abscesses, meningitis and cholecystitis, paratyphoid bacteremia or paratyphoid fever, and gastro-intestinal infections comprising gastro-enteritis and cholera nostras. Until the advent of systematic bacteriological examination of the blood and feces, the more generalized infections of this group were classed, respectively, as food poisoning, cholera nostras, and authentic typhoid fever. The paratyphoid infections are caused by a group of microorganisms lying intermediate between Bacillus coli and Bacillus typhosus. The majority of these intermediate forms are more like the colon bacillus in cultural characteristics and in pathogenic properties; they differ from the typhoid bacillus not so much in their pathogenicity for man as in their superior pathogenicity for animals. Certain of the bacteria of the paratyphoid group affect animals only, so far as is known; others both man and animals; and still others of the group lying nearest biologically to the typhoid bacillus resemble the latter organism in producing only human infections.

We are primarily concerned here with the paratyphoid infections of man, and more particularly with that type of human paratyphoid that resembles typhoid fever most closely. No proper appreciation of human paratyphoid infections can be gained, however, without a survey of the paratyphoid group of bacteria in general, whether primarily pathogenic for man or animals. The presentation of the exact relationship between human and animal diseases in this group is difficult not only owing to their relatively considerable number but to our ignorance of the exact biological relationship between their respective causative microorganisms. A schematic presentation of the more important bacteria of this group in relation to disease may be introduced at

this point to facilitate discussion. The following table (Table XXII) is drawn largely from the complete and recent treatise of Uhlenhuth and Hübener.

TABLE XXII

GENERAL RELATIONS OF BACTERIA OF THE INTERMEDIATE OR PARATYPHOID GROUPS TO HUMAN AND ANIMAL DISEASE

Microorganism	*Animal Infections*	*Human Infections*	*Organism First Described*
Salmonella Group			
B. paratyphosus B.	Primary or secondary septicemia in cattle and horses. Present in intestines of normal animals	1. Gastro-enteritis; 2. Choleriform disease; 3. Typhoidal bacteremia; 4. Local infections	Achard & Bensaud 1896
B. cholerae suis	Secondary invader in hog cholera	———	Salmon & Smith[2] 1885
B. typhi murium	Epidemic enteritis and septicemia in mice	Gastro-enteritis; Typhoidal bacteremia	Löffler[2] 1890
B. icteroides	———	Secondary invader in yellow fever	Sanarelli[2] 1897
B. psittacosis	Epidemic enteritis in parrots	Typhoidal disease Pneumonia	Nocard. 1892
Various bacilli. Some of this group	Dysentery and septicemia in calves	———	———
B. nodulifaciens	Localized liver necroses in calves	———	Langer. 1904
Gaertner Group			
B. enteritidis	Septicemia, enteritis, or mastitis in cattle	Gastro-enteritis (Food poisoning)	Gaertner. 1888
B. danysz	Epidemic enteritis and septicemia in rats and mice	———	Danysz. 1900
B. paratyphosus A	———	Typhoidal bacteremia; Typhoidal localized lesions	Gwyn. 1898

It appears from this table that the more important microorganisms classified under the general heading of paratyphoid bacilli may be divided into three general groups. These groups have been separated on the basis of cultural and immunological characteristics, to which we shall later refer.

Group I consists of those organisms which have been classified under the general heading of the hog cholera group or salmonelloses, a name given by Lignières in deference to Salmon, who with Smith described the first member of this group in 1885.

Group II comprises two organisms, the Bacillus enteriditis of Gaertner and the bacillus of Danysz.

Group III contains Bacillus paratyphosus alpha.

As we shall later see, separation between the first and third groups or their type organisms, Bacillus paratyphosus beta and Bacillus paratyphosus alpha, is easy on the basis of both constant cultural and immunological differences. The separation between organisms of the hog cholera group and of the enteritis group is by no means so easy. Individual members in these groups differ culturally, but there is no constant cultural difference which would make it possible to place a new organism in one group rather than the other. By means of absorbed specific immune sera, however, it may be shown that constant differences really exist between the two groups. All of the organisms considered under these three headings lie biologically intermediate between the colon bacillus and the typhoid bacillus, the hog cholera group of organisms being most like the colon bacillus, and the paratyphoid alpha organism being very close to the typhoid bacillus. These relations are maintained on immunological grounds as well as through cultural characteristics. Similar differences between the organisms at the two extremes are likewise evident in their respective pathogenic properties. The colon-like organisms differ from the typhoid bacillus and the paratyphoid alpha bacillus in that they are not only experimentally more pathogenic for animals, but produce spontaneous disease in them, particularly in cattle, in the nature of enteritis and septicemia. These animal diseases may occur in epidemic forms, as in the case of calf dysentery, mouse typhoid, and the psittacosis of parrots; or they may be secondary septicemias, as in the case of hog cholera. The microorganisms further produce localized inflammatory, purulent, or necrotic processes, as in the case of Bacillus enteriditis, which produces mastitis in cows, and the bacillus nodulifaciens, which is the cause of localized liver necrosis in calves.

In man the colon-like organisms are less frequently the cause of disease than the true typhoid bacillus, and the diseases they do produce in man are more frequently similar to the animal diseases than to true typhoid fever. Human infections may be produced by the colon-like organisms in the form of enteritis, which is, properly speaking, an intoxication and often so severe as to be choleriform in nature, or else in the form of a true infection resembling typhoid fever; or, again, as with the typhoid bacillus, in the form of localized lesions such as pyelitis, cystitis, meningitis, appendicitis, cholecystitis, and pneumonia (Bacillus psittacosis).

The paratyphoid alpha bacillus is not only culturally very

close to Bacillus typhosus, but resembles it in its pathogenic properties. So far as is known, it does not produce a spontaneous disease in animals, and the human infection which it causes is an infection like typhoid fever.

We are concerned in this treatise primarily with the bacteremia of typhoidal type, which several of these intermediate organisms may produce. The paratyphoidal fevers, first of all, resemble true typhoid fever in practically all particulars; secondly, they present certain interesting problems of transmission which differ from the characteristic modes of transmission in true typhoid; thirdly, the paratyphoidal fevers are of interest in connection with the problem of immunization against typhoid, since, as we have already shown, protection against the one disease does not offer security against the other, although the same method applied in paratyphoid that has been utilized in typhoid will doubtless produce similar successful results; and, lastly, the paratyphoidal fevers are found of increasing importance owing to the information that has been gained of their distribution and prevalence in the present world war.

The more characteristically paratyphoidal type of human infections, the gastro-enteritis, also finds its analogy in certain forms of true typhoid fever, as we have already mentioned. Certain of the milder forms of typhoid fever, as for example the French "embarras gastrique febrile" and the mild intestinal upsets occurring in children due to this organism, are cases in point. The choleriform type of paratyphoid infections is more strictly characteristic. Localized infections occur in perhaps greater frequency with the paratyphoid infections than in true typhoid, although in no characteristically different situations.

Our discussion of the relation of paratyphoid infections to typhoid fever narrows itself not only to consideration of the bacteremic type of paratyphoid infection, but also to the particular consideration of only two of the microorganisms mentioned as the cause of human or animal disease. We shall concern ourselves largely with a discussion of Bacillus paratyphosus alpha and Bacillus paratyphosus beta in their relations to the true typhoid bacillus. These two paratyphoid organisms produce the majority of human paratyphoid bacteremias. Exceptions, however, should be allowed in this statement and will probably increase with greater frequency as our ability to differentiate the causative microorganisms increases. A number of forms of paratyphoid bacilli intermediate between the alpha and the beta type have been described, as for example in recent years

the organism isolated by Ohno, the bacteria described by Sarrailhe and Clunet,[2] which produced an epidemic in the Dardanelles, and the organism described by Daumezon. Other closely related organisms, as Bacillus fecalis alkaligenes, have also been found to give rise to generalized typhoidal infections. A further group of infections of this nature, due apparently to a micrococcus (M. typhoideus), have been described by Sartori, Spillman and Lasseur, and by Bourges, Lancelin and Jolly.[1, 2] In considering the general infections due to members of the paratyphoid group of bacteria, it should be mentioned that not only may any one of the organisms be the cause of a disease, but that a mixed infection of typhoid and paratyphoid may occur, as in the cases reported by Gerard and Fenestre, and by Castellani.[10]

CLINICAL DIFFERENTIAL DIAGNOSIS OF PARATYPHOID FEVER

It seems certain from our present knowledge that no differentiation between the paratyphoid fevers and typhoid fever was made before the era of bacteriological examinations, although claims to the recognition of such a form of disease separate from typhoid have been made in retrospect by some observers. With the increasing body of information that has come, particularly in the last few years, in respect to cases of paratyphoid fever that have been authenticated by bacteriological analysis, it appears that certain minor clinical differences between paratyphoid and typhoid fever may be noted. Although fairly consistent for the paratyphoid group in general, these differences are not any greater than might occur between individual cases of typhoid fever, and could certainly never be used for the purpose of differential diagnosis of the one disease from the other in any given case. Fortunately, differential diagnosis is not primarily essential, except in so far as recognition of the relative importance of paratyphoid fevers is concerned, and in the elaboration of specific measures of prevention. As far as the individual case is concerned, the treatment and prevention of extension of the disease is the same in paratyphoid as in typhoid fever.

The main points of differentiation between paratyphoid and typhoid fever have been repeatedly emphasized by the recent work, principally of French observers, during the war conditions in Europe. In general, the paratyphoid fevers are less severe infections than typhoid. The initial symptoms of paratyphoid fever resemble typhoid closely and are characterized by insomnia, headache, epistaxis and nausea. The onset of the disease in para-

typhoid is more frequently abrupt than in typhoid, and is often accompanied by vomiting and by chills. The gastro-intestinal symptoms in general in paratyphoid are more marked throughout the disease than in typhoid fever. The temperature in paratyphoid usually rises more sharply than in typhoid, has a shorter fastigium, and is in total duration notably less on the average than is the case in typhoid fever, the disease usually being under two weeks in duration.

Severe occipital pain is a common symptom in paratyphoid. Dicrotism of the pulse is less frequent than in typhoid. Herpes, both about the lips and in the mouth, are of characteristically frequent occurrence. The mental condition in paratyphoid usually fails to show the characteristic typhoidal state, although meningeal involvement is more frequent than in the true typhoid fever. The liver is more enlarged in paratyphoid, but the spleen less notable than in typhoid fever. Jaundice is a frequent symptom and may occur as the predominating symptom in certain epidemics (Sarrhailhé and Clunet). Sweating is frequent in paratyphoid, and the rose spots distinctly more frequent in occurrence than in typhoid fever. They were found by Robinson in sixty per cent of his cases, and may become confluent and even persist after apyrexia.

The complications of paratyphoid differ only in relative proportion from those in typhoid. In general, recent work has shown that complications may be as frequent and severe as in true typhoid fever; for example, Nobelcourt and Peyre found complications in 38.8 per cent of their paratyphoid alpha cases, in thirty per cent of the typhoid cases, and in 23.6 per cent of the paratyphoid beta cases. As already mentioned, meningitis is not infrequently observed (Sacquépeé, Burnet and Weissenbach; Tolmer and Weissenbach; Daumezon [illegible]). Hemorrhage occurs in five to six per cent of cases. Phlebitis (Minet), pyelitis (Korezynski), epididymitis (Giroux), and myocarditis have recently been emphasized as of relatively frequent occurrence. Peritonitis may occur with or without perforation. Perforation itself is apparently as frequent as in typhoid fever. Relapses occur as frequently as in true typhoid. Thus, Rimbaud, and Coyon and Rivet had relapses in ten per cent of their cases.

Previous to the present war conditions the mortality from paratyphoid fever was extremely low, although the number of cases which serve as a basis of comparison was extremely small. Estimates as low as one per cent of mortality have been given by various authors. More recent work would tend to show that the

mortality from paratyphoid, although lower than from typhoid, is somewhat higher than has generally been assumed. Labbé,[2] for example, had a mortality of five per cent with paratyphoid and of twenty-five per cent with typhoid, and in a later series [3] a closer correspondence of eleven per cent for paratyphoid and fifteen per cent for typhoid. The total mortality due to the two diseases during the present war has, of course, been diminished by anti-typhoid vaccination, which has sharply decreased not only the incidence but the percentage mortality in true typhoid.

The pathological anatomy of paratyphoid fever as compared with typhoid is interesting and somewhat characteristic. In the earlier cases that came to autopsy, as for example the one described by Longcope,[3] no lesions were found in the intestine suggesting typhoid fever. Later and more extended observations, particularly in recent years, have shown that the lesions characteristic of typhoid may also be produced by the paratyphoid infections, although in general the lesions in paratyphoid would seem to extend indiscriminately to the solitary follicles as well as to the agminated follicles of Peyer in the small intestine, and in a recent series of cases have been found in the colon as well (Sacquépée, Burnet and Weissenbach; Grenet and Fortineau). The spleen, as noted under the clinical characteristics, is swollen, although not so markedly as in typhoid.

THE LABORATORY DIAGNOSIS OF PARATYPHOID FEVER

Significant and characteristic as are these clinical variations of paratyphoidal infections from true typhoid fever when cases are viewed in aggregate, they offer little security in the diagnosis of any particular case of a disease of this type. A differential diagnosis of paratyphoid infection depends, as in the case of typhoid fever, on laboratory examinations. The paratyphoid bacilli are found in instances of the disease which they cause, very much as is the typhoid bacillus in typhoid fever, that is to say, in the blood, the stools and the urine. In the case of localized lesions the organism will, of course, be found in the affected locality.

At this point it may be well to refer briefly to the historical evidence on which our present conception of the bacteriology of human paratyphoid infections is based. First, to mention two of the paratyphoid organisms, which, although not concerned with the type of human infection we are primarily considering, are yet of historical interest as giving a basis of classification for subsequently isolated microorganisms. Salmon and Smith described

the hog cholera bacillus in 1885, an organism which they found constantly in the intestines of swine dead of the disease in question, and which at that time was supposed to be the causative agent in the disease. It has subsequently been shown that it is a secondary invader and that the real cause of hog cholera is a filterable virus. In 1888 Gaertner isolated an organism (Bacillus enteritidis) from diseased beef and from the intestinal contents of fifty-seven cases of meat poisoning that had been caused by eating this contaminated food.

In 1896 Achard and Bensaud isolated an organism, which they denominated Bacillus paratyphosus, from the localized lesions subsequent to supposed attacks of typhoid fever in two human beings. This organism has since been shown by subsequent comparative studies to be identical with Bacillus paratyphosus beta. Gwyn in 1898 isolated an organism from the blood in a case of typhoidal disease which differed from the typhoid bacillus in certain particulars and was agglutinated by the patient's serum, which serum failed to agglutinate a true typhoid bacillus. This organism he named Bacillus paracoli, although subsequent examination showed that it is identical with the organism subsequently differentiated as Bacillus paratyphosus alpha. In 1900 Schottmüller [2] in his study of the bacteriology of typhoid described five cases from which he isolated organisms that differ from the true typhoid bacillus. He further separated these paratyphoid organisms into two groups, which subsequent study has shown to be the alpha and beta groups that we have discussed.

Blood Cultures in Paratyphoid Cases

Blood cultures are of preëminent value in the diagnosis of paratyphoid infections as in true typhoid fever, and are made in the same way. The organisms are somewhat more difficult to obtain in paratyphoid cases, owing to the fact that they are present in the circulating blood for shorter periods of time than in typhoid fever. On first examination of blood cultures in paratyphoid infections the organisms present, motile, plump, Gram-negative rods, give no differential indication of whether one is dealing with typhoid or paratyphoid bacilli. The identification remains for subsequent examination, as will be described. Stool cultures are also made in a similar way to cultures in typhoid fever, and the paratyphoid colonies are not markedly different from typhoid colonies on the more important differential media, Endo or Conradi-Drigalski, for example, but may be sharply

differentiated from the colon organisms, for which purpose these media are devised.

TABLE XXIII

DIFFERENTIAL BACTERIOLOGICAL CHART

Method	*B. Typhosus*	*B. Paratyphosus A.*	*B. Paratyphosus B.*	*B. Coli*
Odor	Not significant	Slight	*Fecal. Disagreeable.*	*Fecal*
Motility	Motile	Motile	Motile	*Usually but not always motile*
Broth	No pellicle	Pellicle	Pellicle	Pellicle
Potato (acid)	Moist, glistening, brownish, not very visible	Moist, glistening, not very visible	Thick, brownish, sometimes scanty	Projects; yellow or brownish
Artichoke	No change in color	Little or no change in color	*Green in 2 or 3 days*	*Green rapidly*
Litmus milk	Slight acidity	Slight acidity	*Slight acidity, then alkaline. Ammonia formed*	*Coagulation. Strong acid in 24 hours*
Lactose, Raffinose, Saccharose, Glucose, Levulose, Maltose, Galactose, Dulcite, Mannite	No acid. No gas	No acid. No gas	No acid. No gas	Acid. *Gas*
Neutral red Glucose agar	*No change*	Decolorized fluorescence. Gas	Decolorized fluorescence. Gas	Declorized fluorescence. Gas
Na sulphite fuchsin (Endo)	Colonies colorless	Colonies colorless	Colonies colorless	*Red colonies*
Lit. lactose crystal violet (Conradi-Drigalski)	Blue, transparent	Blue, transparent	Blue, transparent	*Red, opaque*
Subacetate of lead	Blackened	*Not blackened*	Blackened	*Not blackened usually*
Indol	No	No	No	*Yes*

The differentiation of paratyphoid from typhoid bacilli depends on the second step in bacteriological examination and is rendered possible by constant cultural differences in these microorganisms from either the typhoid bacillus or the colon bacillus. In the case of stool cultures separate non-acid-forming colonies and in the case of blood cultures subcultures on agar from an apparently pure growth are subsequently inoculated on the various differential media. The most important differential characteristics are evidenced in the bacteriological chart in Table XXIII, which shows the cultural reactions of Bacillus typhosus, Bacillus paratyphosus alpha, Bacillus paratyphosus beta, and Bacillus coli. The reactions of most diagnostic significance are printed in italics, and it is seen that paratyphoid bacilli may be differentiated from typhoid bacilli, first of all, by their greater fermentative properties in certain of the sugars, glucose, levulose and maltose in particular, and that Bacillus paratyphosus beta may be differentiated from Bacillus paratyphosus alpha by a

characteristic formation of alkali in milk. A more recent method of differentiating Bacillus paratyphosus alpha from Bacillus paratyphosus beta, and indeed from the typhoid bacillus, rests on a characteristic reaction in media containing subacetate of lead, as described by Levy and Vallery-Radot. The accuracy both of this reaction and of the characteristic formation of a green-colored growth on artichoke described by other French authors we have been able to verify in our laboratory. Krumwiede, Pratt and Kohn find that Bacillus paratyphosus alpha differs consistently from Bacillus paratyphosus beta in failing to ferment xylose. The most important method of differentiation of paratyphoid from typhoid bacilli depends, however, on the agglutination by a corresponding specific immune serum. For differential purposes of this sort antisera prepared by immunizing rabbits with Bacillus typhosus, Bacillus paratyphosus alpha and Bacillus paratyphosus beta should be on hand in every laboratory. The titer of such antisera should be relatively high, one to ten thousand or twenty thousand, and an organism to be classified in any group should agglutinate well up toward the titer limit of the serum. All examinations of this sort should be carried out by the macroscopic method, as already described under the diagnosis of typhoid fever. J. Henderson Smith has described an abbreviated method leading to the diagnosis, particularly in stools, of paratyphoid and typhoid bacilli from Bacillus coli and other bacteria in the following manner:

The colon group is eliminated by ruling out organisms which ferment lactose.
The proteus group is ruled out by eliminating organisms which liquefy gelatin.
Acid and gas formation on mannite serve to separate paratyphoid and Gaertner organisms from the typhoid group.

The subsequent differentiation of members of this group would depend on the use of an immune serum as described. Bacillus paratyphosus beta is separable from Bacillus enteriditis of Gaertner only by the use of absorbed specific antisera; that is to say, an anti-Gaertner serum treated by Bacillus paratyphosus beta will still agglutinate the Gaertner bacillus, whereas if the organism in question proves to be a Gaertner bacillus, its addition to Gaertner immune serum will leave no further agglutinins for the authentic Gaertner bacillus.

Diagnosis of Paratyphoid Infections by Means of Agglutination Tests

There is considerable difference of opinion at the present time as to the absolute differential diagnostic value of agglutination tests in paratyphoid fever. The difficulties in drawing conclusions from agglutination tests in the case of typhoid fever have already been insisted on, and in paratyphoid infections, particularly in their differentiation from true typhoid, the difficulties are still greater. The results are complicated, as in typhoid infections, by the possibility of previous vaccination, although a positive paratyphoid agglutination test in typhoid vaccinated individuals is of more diagnostic significance than a positive typhoid agglutination test. The second difficulty is brought about by the fact that the paratyphoid beta organism is more readily agglutinable than either the typhoid bacillus or paratyphoid alpha. The main difficulty in differential diagnosis lies in the occurrence of group agglutinins. Group agglutinins are more likely to be present in a case of true typhoid than in paratyphoid infections; that is to say, the serum of a true typhoid case will more frequently agglutinate paratyphoid bacilli, as well as the causative organism, than under opposite conditions. A certain number, probably from eight to ten per cent, of all true typhoid cases give positive reactions with one or both of the paratyphoid organisms. In the majority of typhoid cases, however, group agglutinins for the paratyphoid bacilli are absent. Whenever a serum agglutinates the typhoid bacillus best, it may safely be assumed that one is not dealing with a paratyphoid infection, although the reverse is not true.

The paratyphoid alpha bacillus is less readily agglutinable than the paratyphoid beta bacillus. For that reason positive reactions to this organism are of greater diagnostic significance. Agglutinins as low as 1 to 40 dilution are of diagnostic significance, which is not the case in cases of paratyphoid beta infection. Both the typhoid organism and the paratyphoid beta organism may, however, be agglutinated by the serum of a case of paratyphoid alpha infection, the typoid bacillus more frequently.

Bacillus paratyphosus beta is, as we have stated, more readily agglutinated than the other two organisms under consideration. For that reason a positive reaction to be indicative of infection with this microorganism should be obtainable in relatively high dilutions. Dilutions as high as 1 to 40,000 are not infrequently obtained and the percentage of positive results is relatively high

in true cases produced by this organism. Courmont, Chattot and Pierret obtained a positive reaction in eighty-eight per cent of their infections due to this microorganism, whereas they obtained it in only thirty-three per cent of the paratyphoid alpha infections, and then in relatively lower dilutions. The serum of a paratyphoid beta case less frequently gives group reactions with Bacillus typhosus and Bacillus paratyphosus alpha. Inasmuch as both typhoid serum and paratyphoid alpha serum agglutinate paratyphoid beta to some extent, a negative reaction to this latter organism by any given serum is presumptive evidence against its being derived from a paratyphoid beta case.

Doubtless the lack of confidence in differential diagnosis of this group of infections by means of the agglutination test is dependent to some extent on the method employed. We have already mentioned under the diagnosis of typhoid fever that the macroscopic test should in all instances be used as more accurate and as presenting no greater technical difficulty than the less accurate microscopic method. Formalinized standard cultures of the different organisms are preferable. A method such as the one recommended by Dreyer should be employed, the end reaction determined, and particular note of the rise in agglutinins to any particular organisms made on successive examinations.

Mixed infections may, as we have mentioned, occur and a positive agglutination reaction with two or more organisms of this group may be due not to the presence of group agglutinins but to the occurrence of separate agglutinins for each infecting organism. In suspected cases of this sort Castellani's [3] absorption method may be employed, although in most hands it has not been found as useful for diagnostic purpose with the serum of patients as under experimental conditions when a high titered immune serum is employed.

THE INCIDENCE OF THE PARATYPHOID FEVERS

In statistics referring to the relative prevalence of paratyphoid fever as compared with typhoid fever, it is somewhat difficult to decide whether data referring to the purely gastro-enteric cases of paratyphoid infection have been included or should be included. It would be perhaps most useful, particularly in a discussion like our own, to rule out all purely gastro-intestinal attacks, inasmuch as they may be caused not only by members of the paratyphoid beta group of organisms and by the separate Gaertner enteriditis group, but by such organisms as Bacillus pyocyaneous, the colon

bacillus and the toxins of Bacillus botulinus. Paratyphoid fever has been described in practically all localities of the world, and may be considered as widespread as true typhoid fever. Numerically, however, the paratyphoid infections, even if we include the gastro-enteric attacks where paratyphoid bacilli have actually been isolated from the stools, are greatly inferior to the true typhoid cases. In Germany, where most of the statistics have been obtained and where the disease is most prominent, Klinger [2] found that in the southwest in the years 1906 to 1907 there were only 307 paratyphoid cases to 3560 true typhoid cases, or something like ten per cent. In other statistics from Prussia quoted by Uhlenhuth and Hübener, and which were bacteriologically proved, there were from the years 1906 to 1909, 1662 paratyphoid cases as against 57,955 typhoid cases, only about three per cent. In England, Boycott estimates that three per cent of the enteric cases are due to paratyphoid bacilli.

The relation of Bacillus paratyphosus alpha to Bacillus paratyphosus beta, in respect to number of infections produced, would seem to vary considerably in different countries. In Germany statistics show that there are fully ten times as many paratyphoid beta cases as paratyphoid alpha cases. Sacquépée and Chevrel collected five hundred authentic cases of paratyphosus beta infections, but only twelve cases of paratyphosus alpha infections from the literature. Bainbridge states that paratyphosus alpha is, on the other hand, much more frequent in India than the paratyphosus beta infections, and this relation has usually been regarded as holding also in the United States. For example, Chamberlain found that the majority of cases on the Mexican border in the year 1916 were due to Bacillus paratyphosus alpha, 245 alpha cases being described to five paratyphoid beta.

During the present world war numerous systematic studies have been made in France as to the relative occurrence of these two paratyphoid infections in French troops. It is interesting to repeat that the effect of antityphoid vaccination has been to reduce enormously the number of typhoid cases, so that the paratyphoid cases markedly predominate, the exact reverse of all previous relations, as we have stated. The total number of cases of typhoid and paratyphoid fevers has also been markedly reduced, owing to the prevention of the true typhoid infections. The relative proportions of paratyphoid alpha and paratyphoid beta infections have apparently varied from time to time. Thus, Coyon and Rivet, and Grenet and Fortineau [2] found in their cases that paratyphoid alpha infections markedly predominated

in the early part of the war, 124 of the alpha infections being listed in their combined reports to thirty-one of the paratyphoid beta infections. More recently, however, Labbé [3] and Bernard have found an almost reverse proportion of 107 beta cases to thirty-nine alpha cases. In a similar manner Archibald, Hadfield, Logan and Campbell have noted a sudden change from paratyphoid beta fever to paratyphoid alpha in the Dardanelles. The change in the relation of these two organisms in Continental Europe may to some extent be explained by two facts. In the majority of statistics the food poisoning infections have in the past been included among the data, and these are due to the beta type of infection; and, again, diagnosis based on the agglutination test would tend to increase the number of beta infections, owing to the greater agglutinability of this organism than of paratyphosus alpha. These two facts would indicate that the paratyphosus alpha cases may have been more frequent than is indicated by the earlier figures we have given. During the war, in addition, the source of infection would be a matter of considerable importance. It is probable that the majority of infections were produced by drinking contaminated water, which is more particularly a mode of transmission of the alpha type of infection, as it is of true typhoid, than of the paratyphosus beta infections.

Paratyphoid fever resembles typhoid fever in its general distribution in reference to season, age and sex. There is not so sharp an increase in paratyphoid infections during the summer, as is the case with typhoid fever. Both sexes are equally susceptible, and apparently the greatest incidence in paratyphoid, as in typhoid, occurs between fifteen and twenty years of age.

EPIDEMIOLOGY IN PARATYPHOID INFECTIONS

Investigations have shown that in general paratyphoid infections follow much the same modes of transmission as does true typhoid fever, with certain notable exceptions. The order of importance in the agents of transmission would seem to be somewhat different in paratyphoid than in typhoid infections. Food stuffs are the most important methods of conveying infection in paratyphoid infections, and contact and water follow after them, whereas contact and water are the more important modes in the transmission of typhoid fever. This greater importance of food stuffs is due primarily to the fact that in infections of the paratyphoid beta group animals are vitally concerned in the transmission, which is not the case in typhoid or paratyphoid alpha

fever. We have already referred to the important group of food poisoning cases which may be due either to Bacillus enteritidis or to Bacillus paratyphosus beta. The importance of these cases is suggested by the number collected by Ostertag as occurring in Germany from the years 1880 to 1900. He found during this period eighty-five epidemics of food poisoning with more than 4000 cases. There are many more of these infections in Germany than elsewhere. Pork, beef and veal are the most frequent sources of food poisoning, owing to the characteristic diseases in animals which the paratyphoid organisms produce. These diseases are transmissible in the meat, particularly when it is not fully cooked, and infection of the meat takes place more frequently by intravital infection of the animals concerned; that is to say, by the utilization of the meat of diseased animals and, secondarily, by the contamination of butchered meat through handling. Food poisoning is rendered possible not only by the fact that the paratyphoid bacilli remain living and may multiply in the diseased meat unless it is thoroughly cooked, but by the fact that they produce toxins which are more resistant than the bacteria themselves. In general, it may be said that the paratyphoid bacilli are slightly more resistant to external agents than the true typhoid bacillus.

The transmission of paratyphoid fevers through contaminated meat is rendered possible not only by the fact that they are the cause of a number of infections in animals, but also by the fact that they occur in the intestines of healthy animals, particularly in swine, cattle and rats and mice, particularly those that have fed on the refuse from slaughter houses. It has also been claimed that paratyphoid bacilli may be found in the intestines of healthy men, but there seems no reason for supposing that their occurrence there in the two to six per cent of cases in which they have been reported by some observers, represents any more than the healthy carrier condition, which has also been recognized to occur in typhoid fever. It is probable that healthy carriers of paratyphoid bacilli may be more frequent, owing to the fact that they are less likely after ingestion to produce a recognizable infection than the true typhoid bacillus.

PROPHYLAXIS OF PARATYPHOID INFECTIONS

The prophylaxis of paratyphoid infections rests in the measures that are taken against true typhoid infections and in the additional precautions as to the thorough cooking of meat and care

in handling meat after butchering. The precautions that should be taken to avoid human carriers of typhoid infections also obtain in the case of paratyphoid infections. It has been shown by Hilgerman, for example, that 3.6 per cent of recovered paratyphoid cases remain carriers, and healthy carriers have also been described by Prigge and Sachs-Müke. Krumwiede found four per cent of healthy carriers in 786 men in the 14th Infantry, N. G. N. Y., after its return from Texas. As in the case of typhoid infections, the gall bladder remains the main seat of multiplication of the bacilli and a focus for further transmission of the disease. Paratyphoid bacilli have also been found in gall stones, bone abscesses and periostitis, as in the case of typhoid fever. Urinary carriers have likewise been described in a few cases. Autoinfection of paratyphoid carriers has been shown to be a possibility by Prigge and Sachs-Müke.

CHAPTER XIII

THE TREATMENT OF TYPHOID FEVER

This treatise is in no way designed to serve as a clinical manual. We are interested, therefore, under the heading of Treatment of Typhoid Fever, not so much in discussing the various remedies that have been suggested for the alleviation of the symptoms, or meeting the complications of the disease. The majority of remedies of a medicinal sort have been merely palliative and have had little influence in modifying the course of the disease. The importance of surgical interference in typhoid fever, particularly in relation to its complications, has been fully considered by Keen. Our consideration of the treatment of typhoid fever logically limits itself to a consideration of certain types of therapy which may be regarded as really efficacious in modifying the course of the disease or as specific in nature. Although certain of the means of therapy we shall consider, as for example hydrotherapy, were first adopted for empirical reasons, all of them have sooner or later become related to experimental evidence acquired in response to increasing knowledge of the exact mechanism of the disease.

THE INFLUENCE OF DIET IN TYPHOID FEVER

R. J. Graves, 1797–1853, is credited by Cole with having been the first to introduce liberal feeding in typhoid, and the food he advocated was chiefly farinaceous in nature. Other writers since that time have in varying degree increased the ordinary feeding in this disease, which for the most part has consisted of a milk diet. In the last few years much interest and importance has attached to the careful experimental studies on diet in typhoid by Coleman and his collaborators, which seem based on a thorough understanding of the pathogenesis and particularly of the metabolism during this disease. Coleman and Dubois showed that the nitrogen excretion rises and falls with fever, so that in typhoid it is increased to forty or fifty per cent beyond the normal. They found, however, by comparing the metabolism of starving and liberally fed typhoid cases that the increased nitrogen produced by feeding was not more than three to five per cent beyond

the usual increase which occurred during the fever. They conclude, therefore, that food has little or no dynamic action in increasing metabolism. It is important, however, to keep up the nitrogen equilibrium, a failure to do which results in the marked and often extreme emaciation which accompanies the evolution of the disease.

It was shown by Dubois that proteins, fats and carbohydrates are absorbed nearly as well in typhoid fever as under normal conditions, but it is found that the nitrogen equilibrium is not so well maintained by an increase of fat or of protein as when carbohydrates are given in excess (Shafer and Coleman). Coleman,[2, 3] therefore, has recommended and employed a liberal diet of milk, cream, butter, eggs and lactose, and finds that a patient may actually gain weight during the febrile period provided he coöperates and is able to retain nourishment. In a series of 110 cases Coleman found that the average loss of weight was only ten pounds. In a more recent and extensive series totalling 222 cases, Coleman [4] claims that the entire picture of the disease is changed as compared with control cases. Complications are less formidable, the mortality is reduced from fifty to seventy-five per cent and the duration decreased.

It seems possible from the subsequent work of Torrey that a carbohydrate diet is of benefit in the treatment of typhoid, not only as maintaining the nitrogen equilibrium, but also owing to the fact that it tends to modify the intestinal flora. Torrey found fewer typhoid bacilli in typhoid cases that were fed on the liberal diet and an increased number of acid-producing bacteria (Bacillus acidophilus). The suggestion of Collings of the use of Bacillus bulgaricus to produce a similar acid medium and thereby inhibit the growth of typhoid bacilli, which he regards as having produced beneficial effect, is distinctly in line with Torrey's work. According to Torrey, Coleman has actually tried the effect of cultures of Bacillus acidophilus in a few cases. Alvarez has recommended the use of acid drinks. particularly of vinegar, possibly designed to effect a similar purpose. Liefmann's suggestion of sour milk therapy as a means of preventing typhoid carriers has already been mentioned.

HYDROTHERAPY IN TYPHOID FEVER

Hydrotherapy in typhoid, as in other fevers, comprises not only the use of baths and external applications of water, but also the drinking of water and other fluids. The use of water in these ways

has been alternately encouraged and discouraged in the evolution of medical practice. We are told by Cayley (Murchison) that Antonius Musa, a Roman physician, became famous through his treatment of the Emperor Augustus by cold baths when he fell ill of typhoid, and at all events the method must have been practiced in remote antiquity. It was, however, towards the end of the eighteenth century (1797) that Currie first described the benefits which followed the liberal application of cold water in typhoid and typhus fevers. He used for the most part cold sea water, which was poured over the patient, who had been seated for the purpose in a chair. Currie's method gained no considerable vogue until it was revived by Brand in 1861, since which time it has been freely advocated by the majority of physicians who have tried it. There would seem to be a unanimous conclusion in the use of hydrotherapy that at least it is harmless in all conditions of typhoid, except in perforation and hemorrhage, and that it apparently does considerable good. There is distinct evidence that the mortality is lowered, although the evidence is not so definite that the duration of the disease is lessened.

External hydrotherapy in typhoid is practiced in one of three ways: by cold sponges, the cold pack, or by the bath, the latter being the more usual method and the one advocated by Brand. Baths are given usually with water at a temperature of from 65° to 70° Fahrenheit for about fifteen minutes, either when the temperature has risen to 102° or more, or as a routine, irrespective of the height of the temperature, during the febrile period every three hours. The exact temperature of the bath has varied in the hands of different physicians, some preferring to give a tepid bath or bath with a temperature above 70° Fahrenheit, particularly for the first few times. The method should vary a good deal in accordance with its acceptance by the patient.

Apart from its apparent effect in reducing the mortality somewhat in any considerable series of cases, the cold bath acts by reducing the temperature temporarily for a degree or more, which would seem of advantage. It allays the nervous symptoms, increases diuresis and diminishes arterial tension. Although the reduction in the temperature is transitory and not very marked, it would appear to be of temporary benefit to the patient, who usually feels better following its administration. There are two essential symptoms following the bath which we suggest may be of significance in explaining its beneficial effect, an effect which is more marked in other methods of specific therapy which exaggerate these symptoms and through them apparently lead to more

striking results. It is agreed by all observers that the bath to be effective should produce a distinct chill in the individual, and this chill, moreover, is accompanied by a hyperleucocytosis (Thayer).

TREATMENT OF TYPHOID FEVER BY MEANS OF SERA

The possibility of an effective serum therapy in typhoid fever has been long and seriously considered by many investigators, but we find it extremely difficult to pass any judgment, not only on the results that have been obtained, but even on the value of the evidence that has led to the advocacy of the various types of serum employed.

Certain aspects of serum treatment may easily be disposed of before proceeding to a discussion of the more extensive work on the use of various types of immune serum obtained from animals. In two lines of investigation at least the serum of individuals who have recovered or are successfully resisting typhoid infection have been employed in treating the disease. Von Jaksch and Walger were apparently the first to employ the serum of recovered cases of typhoid fever in treatment, and the results they obtained were at least encouraging. This type of treatment has recently been revived by Petrovitch, who was apparently able to reduce the mortality in nearly 500 cases of typhoid by treating them with the serum either of convalescents or of immunized individuals; whereas the mortality in the 487 treated cases was 4.3 per cent, in 1020 controls during the same period it ran as high as 12.8 per cent.

Autoserumtherapy has been recently suggested by Koenigsfeld,[2] and by Ramond and Goubert. Koenigsfeld withdraws the blood from a given case of typhoid in considerable amount and subsequently inoculates the individual subcutaneously with his own serum daily in doses of from two and one-half to four cubic centimeters. In fourteen of the eighteen cases treated in this manner the individuals would seem to have been bettered, and particularly those cases that showed a high Widal at the time at which the serum was withdrawn. Ramond and Goubert have treated fifty cases by withdrawing the blood from the vein and immediately injecting it subcutaneously in a neighboring locality. Good results would seem to have followed this method in some thirty-eight per cent of their cases, whereas no effect is claimed in forty-four per cent.

Numerous specific immune sera derived from horses, goats and other animals have been employed in the treatment of typhoid fever. Extraordinarily good results have been claimed by a few observers, although the benefit produced by this method of treat-

ment has in the hands of the majority remained merely encouraging. The immune sera employed have varied considerably in their method of preparation, which has depended on the individual conception of the investigators as to the nature of the harmful results produced by typhoid infection, the type of antibodies that may most logically be used in combatting them, and, finally, the most successful manner of producing these desired antagonistic substances. We have already discussed the question of the nature of the poisons present in or excreted by the typhoid bacillus, than which no subject is more involved in a mass of experimental data, and concerning which little ultimate opinion may at the present time be offered. As we have already stated, it has been known since the time of Brieger and his collaborators that cultures of the typhoid bacillus are toxic for experimental animals, although in the original experiments the possible toxicity of culture media still further complicated the findings. The work of Bandi, Chantemesse,[2] Rodet, Aronson, Meyer and Bergell, Kraus and Stenitzer, and Yamanouchi would indicate that true soluble toxins are produced by the typhoid baccillus under favorable conditions of temperature and culture medium, although these toxins in no wise approach in strength and importance the true exo-toxins, such as those produced by tetanus and diphtheria bacilli. On the other hand, beginning with the work of Pfeiffer and Kolle,[2] 1896, a growing series of observations by Martin, McFadyean and Roland, Sanarelli, Conradi,[6] Balthazard, Besredka and others would attribute a major importance to the endo-toxins derived from the bodies of the bacilli rather than to any products formed in their growth. We have already stated our opinion that no sharp differentiation in the essential nature or properties can be drawn between the endo- and exo-toxins. It would appear that the occurrence of the soluble toxin would depend simply on the strain of bacteria used, and the ease with which the toxin is eliminated, which in turn depends largely on the culture medium employed. This point of view is rendered probable by the work of Arima [2] and others, which shows that antibodies directed against either the soluble or the endo-toxin, respectively, neutralizes both poisons. The majority of antisera employed in the experimental studies of typhoid infection and in the treatment of typhoid fever have been prepared with the design that they should be antitoxic rather than anti-infectious, in order to produce the desired result. In other words, they have been designed to neutralize the poisons in the typhoid bacillus rather than to promote directly or indirectly the destruction of the bacteria themselves. It is by no means cer-

tain which result should be aimed at in the combatting of typhoid infection, and it is indeed probable that both results have to some extent been realized by many of the sera prepared, independent of the guiding thought that has led to their preparation. It is probable that an immune serum formed in response to the injections of living or dead bacteria will differ only in degree from an immune serum produced in response to the injections of extracts of such bacteria, and, indeed, the most successful typhoid antisera which we are about to describe have been produced by injections of both preparations. It may promote exposition to discuss certain of the best-known typhoid antisera without further attempt to outline the principles involved in their manufacture.

Antiserum of Chantemesse

Shortly after his description of a soluble toxin from the typhoid bacillus Chantemesse [2] prepared an antiserum by immunizing horses with this preparation for a long period of time. The virulence of the microorganism was supposedly increased by its growth on a medium containing spleen extract. This serum was subsequently studied in detail by Balthazard, a pupil of Chantemesse, who, however, arrived at the conclusion that the toxins of the bacillus were largely intracellular in nature. Balthazard finds that Chantemesse's serum agglutinates the typhoid bacillus in very high dilution and protects experimental animals, owing to its power of destroying the living organisms and of protecting the leucocytes from the endotoxins. Chantemesse has claimed extraordinary success following the use of this serum. He injects very small amounts, in fact only a few drops, subcutaneously, and one injection is usually all that is necessary. No claim is made that the disease is remarkably shortened, although the temperature usually falls a degree or so within a few days after injection. In 1000 cases, however, the mortality was reduced to 4.3 per cent, whereas in Paris hospitals during the same period seventeen per cent of the untreated cases died. It seems surprising that this serum has not been more generally employed if its results are really as significant as they appear to the author. Josias seems also to have had favorable results with the serum, and no negative evidence to disprove its value has appeared.

Besredka's Antiserum

Besredka [4] prepared an antiserum by immunizing horses against endotoxins which he derives from the typhoid bacillus by drying the cultures, grinding them with salt and then extracting the

poisons. Very little practical results have been reported from the use of this serum, although it has been tested experimentally by Pfeiffer and Bessau,[2] Arima [2] and others. Pfeiffer and Bessau claim to have demonstrated that Besredka's serum is not primarily anti-endotoxic as originally claimed, but does destroy the organisms when injected simultaneously with them in animals. Arima [2] found that Besredka's antiserum would neutralize both the exo- and endotoxins which he has described and differentiated. Andriescu and Ciuca found that on administering this serum intravenously in human cases the microorganisms disappeared rapidly from the circulating blood. Montefusco apparently obtained some benefit in a few serious cases with Besredka's preparation.

An anti-endotoxic serum from goats has also been used by Ludke [2] with good results in a few cases of typhoid. The antitoxin produced by Kraus and Stenitzer by immunizing animals with their soluble toxins has apparently been used to some advantage in sixteen cases by Gaupp, who administered the serum intravenously. Serum has been prepared also by immunizing animals with sensitized cultures of the typhoid bacillus by Garbat and Meyer and by Karaffa-Korboutt. Garbat and Meyer give good experimental evidence which led them to anticipate better results from a mixture of sera of animals that had been immunized on the one hand with sensitized bacteria and on the other with untreated typhoid bacilli. Their contentions, however, did not seem to be borne out in practice by Rommel and Hermann. Perhaps the most encouraging results that have been obtained by serum therapy in typhoid have been in the hands of a number of French observers, who have employed a serum prepared by Rodet,[2] who immunized horses intravenously both with living bouillon cultures and with old endotoxins from the typhoid bacillus. The results of treatment with this serum have been reported on favorably by Rodet and Lagriffoul, Rémond and Minvielle, by Étienne and by Rodet himself. Rodet [3] summarizes the results in 400 cases and finds that repeated injections of this serum in doses of from ten to twenty cubic centimeters given subcutaneously every other day result in markedly decreasing the duration of fever in cases that are treated early in their course, and may lead to an abortive cure in six or eight days in the most favorable of them. Étienne obtained similar results in some 200 cases. In short, this serum would seem the most favorable one hitherto described, and its mode of action suggests certain analogies to, although less striking results than those obtained by the use of vaccines, to a consideration of which we may now turn.

VACCINE TREATMENT IN TYPHOID

In 1893, Eugene Fraenkel began treating cases of typhoid fever by subcutaneous injection of killed cultures of Bacillus typhosus, and obtained results which to his mind were encouraging. Little interest was at first awakened by Fraenkel's work, except in relation to the specificity of the treatment by Rumpf and others, to which reference will subsequently be made. In 1902, Petruschy [2] used a combination of vaccine and immune serum in typhoid, and in 1908 Pescarolo and Quadrone advocated the use of living avirulent cultures. Following the interest in vaccine therapy awakened by Wright, increasingly frequent reports on the possible value of typhoid vaccines in typhoid fever have appeared. In 1912, Callison summarized the results obtained by numerous authors, chiefly English and American, in 747 cases, and in 1915, Krumbhaar and Richardson could collect over 1800 cases reported on by forty authors. The original method prescribed by Fraenkel, the subcutaneous injection of killed typhoid cultures, is apparently being used with increasing frequency by physicians. The best studied groups of cases treated in this manner, however, give ground for little unrestrained enthusiasm as to results produced, and certainly no claim is made that anything approaching a specific type of therapy has been obtained by this method. The majority of physicians would seem to be following blindly certain general ideas of vaccine therapy that have tardily permeated the clinical world through the work of Wright. The best that may be said is that Fraenkel's vaccine therapy in typhoid may cause a shortening of the course of the disease, a lower mortality, and probably also fewer relapses and complications. The demonstration of these beneficial effects is, however, difficult in any particular series of cases, owing to the necessity of the employment of statistical methods which include as a prerequisite large numbers of cases and adequate controls, such as are rarely or never obtained in the experience of any one investigator. We shall attempt an analysis of the results of recent workers who have employed this method, after having described certain radical modifications in it which we believe have led to a far more specific type of therapy.

In the last four years two modifications have been made in the use of vaccines in typhoid, which have furnished results in a large and growing group of cases that may be regarded as strongly indicative that a specific type of therapy is being arrived at in this disease. We use the expression "specific" here in its largest

sense of "definite," and not in the narrower bacteriological and immunological sense which correlates some definite result with the specific etiological agent in the disesae. The results which we shall describe are, at least in part, due to a non-specific protein reaction, which may be produced at least to some degree by the employment of a number of proteins which have no relation to the typhoid bacillus. The two innovations in Fraenkel's method, to which we have referred, are, first, the injection of the vaccine intravenously, and, secondly, the use of sensitized in place of ordinary untreated vaccine. The first of these innovations would seem more important than the second, although there is very distinct evidence that sensitized vaccines work better than unsensitized, as we have judged to be the case in prophylactic immunization against the disease.

The intravenous injection of typhoid vaccines in typhoid fever was first mentioned by Thirloix and Bardon in 1913, who showed that two to ten million bacteria could be injected in this manner without harm and with much better result than when larger doses were given subcutaneously. This method was further amplified by Ichikawa in the following year, who gave intravenous injections of typhoid bacilli that had been treated and thereby sensitized with the serum of convalescent cases. In addition to a large number of authors who have reported on results obtained by each of these methods, we find an intermediate group who have used sensitized vaccines subcutaneously. We have made a careful and fairly comprehensive analysis of the various reports made in the last five or six years on the use of each of the types of vaccine therapy to which we have briefly referred, and present them as of suggestive value.

TABLE XXIV *

SUMMARY OF RESULTS OBTAINED BY RECENT OBSERVERS (1913–1917) IN THE TREATMENT OF TYPHOID FEVER BY VACCINES ADMINISTERED IN VARIOUS WAYS

	Observers	*Total Cases*	*Estimates based on*	*Benefitted*	*Mortality*
Untreated vaccine subcutaneously	30	1001	512	46%	14.5%
Sensitized vaccine subcutaneously	14	593	239	69%	8.0%
Untreated vaccine intravenously	22	501	233	62%	13.0%
Sensitized vaccine intravenously	12	487	316	85%	11.0%

* The authors referred to in this summary are herewith given, a division being made in respect to the type of vaccine employed and its method of ad-

A careful study of this table will bring out a number of facts which a mere cataloguing of the results obtained by each of the authors quoted could not convey. It will be noted, first, that the most frequent method of vaccine therapy not only has been but continues to be the subcutaneous injection of ordinary and, usually, of heat-killed typhoid bacilli. The results by thirty authors are quoted as contrasted with twenty-two that have used similar vaccines intravenously, and a still smaller number that have used sensitized vaccines either subcutaneously or intravenously. The total number of cases gathered from these various reports would likewise show a predominance of subcutaneous plain vaccine treatments. The reports cited vary markedly in their completeness, many of the writers failing even to give the number of cases they have treated, and others making only the most general report on the results obtained. In the third column are found the total number of cases in each group on which a definite statement has been made as to the number benefitted. The grounds on which a claim of benefit is made are again found to vary markedly, and will be more fully discussed when we come to consider the actual effect of the vaccine injections in each of the types of therapy referred to. The percentage figures, then, under the heading of benefitted must be admitted to be distinctly affected by subjective influences. We believe, however, that they are of more than suggestive value. The mortality figures would not seem to vary strikingly between the groups listed, and to be all within the normal limits of untreated cases, although they cer-

ministration, as in the table. (1) Recent authors reporting on the use of untreated vaccine subcutaneously: 1911, Fletcher; 1912, Sadler, Callison; 1913, Fornet; [2] 1914, Josue and Belloir, Weil, Sacquépée and Chevrel,[2] Guinon and Malarte, Pensuti; 1915, Goldscheider and Aust, Bourke, Evans and Rowland, Feistmantel, Mertz, Peiper, Krumbhaar and Richardson, Groer, Wiltshire and MacGillycuddy, Reiter, Löwy, Lucksch and Wilhelm, Peutz; 1916, Whittington, Zupnik, Müller and Leiner, Waitzfelder. (2) Authors who have employed sensitized vaccine subcutaneously: 1912, Ardin-Delteil, Negre and Raynaud; [2] 1913, Ardin-Delteil, Negre and Raynaud, Roques, Boinet; 1915, Petrovitch, Garbat,[2] Feistmantel, Szecsy, Liebermann, Fellner, Löwy, Lucksch and Wilhelm, Boral, Deutsch; 1916, Galambos, G. Mayer. (3) Authors who have injected untreated vaccine intravenously: 1913, Thiroloix and Bardon; 1914, Kraus and Mazza, Kraus; 1915, Biedl, [1, 2] Ditthorn and Schultz, Csernel and Marton,[1, 2] Reibmayr, Mazza, McWilliams, Holler, Paulicek, F. Meyer,[2] Rhein, Lentz, Ortiz, Acuna and Belloc; 1916, Faginoli, Petzetakis, Zupnik, Müller and Leiner, Löwy, Lucksch and Wilhelm. (4) Authors who have injected sensitized vaccine intravenously: 1912, Ichikawa; 1914, Meyer and Altstaedt; 1915, Biedl,[1, 2] Eggerth, Holler,[1, 2] Sladek and Kotlowski, Koranyi, Landsberger, Löwy, Lucksch and Wilhelm; 1916, Rohonyi, Galambos; 1917, Caronia.

tainly possess an objective value. We believe that the striking difference in percentage which emerges from the statistical study of these authors and cases that we have mentioned, as between those cases treated subcutaneously by ordinary vaccines and those treated intravenously by sensitized vaccines, a difference of nearly one hundred per cent, represents a conservative rather than an exaggerated statement of the importance that has been made in recent modifications in vaccine therapy in typhoid. A discussion of the actual type of benefit produced, or rather of the results which follow in the actual treatment of cases, should now be more fully presented.

The results of our personal experience in the intravenous vaccine therapy of typhoid fever have not been included in the summary presented in the last table, as it seems advantageous to use them as a separate basis of discussion of the results produced by this method of treatment. Our own results vary only in degree from those obtained by the authors we have cited. We were led independently and before the publications of Thiroloix and Bardon and Ichikawa to suggest and later to employ intravenous vaccine therapy for the following reasons (Gay [2]). Certain of the experimental studies of Gay and Claypole [4] in the typhoid carrier condition in rabbits brought out the interesting fact that the injection of typhoid bacilli in immunized rabbits gave rise to a grade of leucocytosis which was to some extent specific. The injection of any foreign protein in an animal produces a transitory leucopenia followed by an increase in the polymorphonuclear leucocytes, and the typhoid bacillus or its extractives produces such a result in normal rabbits. When, however, the same number of typhoid bacilli are injected in a rabbit that has been previously immunized against this microorganism, the degree of leucocytic increase is considerably increased over what occurs in the normal animal. This increased leucocytosis would seem to be due to the presence of immune bodies in the serum of such immunized animals, which act as tropins and render the injected bacteria more attractive for the leucocytes. This would seem to be proved by the fact which Gay and Claypole demonstrated, not only with typhoid bacilli but with red blood cells, that a sensitized antigen will give rise to a higher grade of leucocytosis in normal animals than an untreated antigenic substance. In the case of carrier rabbits it was possible to demonstrate that the production of this specific type of hyperleucocytosis is coincident with the diminution or disappearance of bacteria in the body of the carrier, and it was

therefore suggested that a similar stimulation of leucocytes might be of advantage in treating cases of typhoid fever which are characterized by the diminution in polymorphonuclear leucocytes. It was judged that the type of sensitized vaccine sediment which we had advocated in prophylatic vaccination against typhoid would be most serviceable for therapeutic uses of this sort, not only as stimulating a greater leucocytic response, but as being less toxic than the untreated vaccines. The superiority of sensitized over unsensitized vaccines in treatment would appear evident from the summary of the literature which we have already offered. In addition to the agreement as to the higher percentage of benefit obtained by these vaccines, may be mentioned observations of certain authors who have used both sensitized and unsensitized vaccine in treatment and report better results with the first than with the second preparation. Such conclusions were drawn by Paltauf, Holler, and Feistmantel on the basis of comparative experience with the two vaccines. Our results (Gay,[2] Gay and Chickering, Gay [3]) with the use of sensitized vaccine sediment, although not compared with the use of other vaccines, would seem as successful as any that have been reported.

The intravenous injection of sensitized vaccine sediment produces a series of distinct symptoms which vary markedly in intensity with individuals and with the dose employed. The usual amount on initial injection has been one-fiftieth of a milligram (corresponding to 150 million bacteria), and a corresponding dose in children, who, as in prophylactic immunization against typhoid, react less markedly than adults to corresponding amounts. We shall later refer to the findings of other investigators who have used other vaccines intravenously and who have described alarming or even dangerous symptoms following their employment. It should be noted, however, that our vaccine, owing to its sensitization and the removal of endotoxins, certainly gives less perturbing, and, so far as we have observed, no really untoward effect. It seems necessary to produce a moderate reaction in order to effect the desired result, and the dosage in successive inoculations has been increased slightly in order to produce a similar train of symptoms on each inoculation, which a continuance of the same dose usually fails to do. The injection of the vaccine intravenously is followed in from fifteen minutes to an hour by a chill, which lasts for a few minutes to ten or fifteen. This chill, or shaking, is not accompanied by a feeling of coldness, but rather by a sense of involuntary, spasmodic, muscular

contraction. The chill is accompanied by a rise in temperature of one to three degrees, which reaches its height within three hours after injection and then falls. There may be a rise in temperature without a chill, or the reverse. The rise in temperature is accompanied by a leucopenia, which may fall as low as 2000 to 3000 to the cubic centimeter. The chill is accompanied by an increase in the pulse rate and may be accompanied by slight cyanosis, slight respiratory distress, and frequently a sense of discomfort. According to Scully, the blood pressure rises during the chill and then falls.

The temperature reaches normal or sub-normal in about twelve hours. This fall in temperature is accompanied by sweating, which may be profuse and last for several hours, relaxation, and usually general amelioration of such symptoms as headache, delirium and the like. The patient often feels perfectly well, and this condition, even when transitory, seems beneficial. Coincident with the fall in temperature there occurs a rise in the leucocytes, which may reach as high as 40,000 and which are characterized by a relative polymorphonuclear increase. We shall later refer, in reviewing the work of others with similar methods, to the dangers that have appeared with slightly different vaccine preparations, and to the contra-indications to such injections that undoubtedly exist. We may repeat, however, that in our experience of 1200 injections reactions of this sort have never appeared harmful, either immediately or ultimately, and contra-indications seem, in the light of increasing experience, to grow progressively fewer.

No detailed method of procedure can be prescribed for treating any given case of typhoid fever by this method. The best results seem to be obtained by provoking a distinct but not too severe reaction of the type outlined. The dose necessary to produce such a result varies markedly with the individual and the particular balance already established between the typhoid bacillus and the reaction antibodies in the host. The temporary drop of temperature to normal may become permanent and remain there, in which case no further injections are required, except for the prevention of relapse. If the temperature again rises over a period of two or three days, the injection should be repeated in slightly increased amount, and so on until the desired result is produced or further injections are judged futile. A considerable number of injections may be given with perfect safety. As many as fifteen or sixteen have been given in certain instances, but if no striking result is obtained following three or four injec-

tions at two or three day intervals, very little effect from further treatment may be expected.

It has seemed wise to us previously to separate our cases into three rather definite groups in respect to the results produced by the vaccine injections. We believe that this grouping, based on results produced, is a conservative one and by no means represents all the benefit that attends this method of treating typhoid fever. We have briefly referred to the fact that the temperature excursion with return to normal is accompanied by subjective feelings of well being, although at times of slight weakness, and would seem to be both immediately and ultimately of benefit to the patient. Such subjective amelioration is, of course, open to error in interpretation, but would seem, not only to us but to others who have watched our cases, to be frequent and of a convincing nature. The nurses, for example, in charge of the cases not only volunteer remarks as to the benefit produced by the vaccine injections, but emphasize the lessened care which patients treated in this manner entail. We prefer, however, to base our judgment as to the good results of the method rather on the more objective results that have been produced, the shortening of the duration of the fever, its frequent abrupt termination in an abortive form, the lessening of mortality and of complications in particular. We have classified the three groups of results obtained as abortively recovered, as benefitted, or as unaffected. Cases illustrative of each of these types of result produced by the vaccine injection are given in the reproduced clinical charts in Figures 4, 5, and 6, which are explained in their footnotes.

A summary of our ninety-eight cases classified under these three headings proves of interest not only in respect to results achieved, but as bearing on the mechanism by which it is effected. In Table XXV are expressed certain characteristic findings in each of these groups of cases under consideration, which we may briefly refer to in drawing certain conclusions as to their significance.

TABLE XXV

SUMMARY OF RESULTS IN 98 CASES OF TYPHOID TREATED BY INTRAVENOUS INJECTION OF SENSITIZED VACCINE SEDIMENT

	No. of Cases.	*Age.*	*Widal Titer on beginning treatment.*	*Blood Culture. Positive*	*Treatment begun. Day.*	*No. of treatments.*	*Permanent Normal.*	*Days of treatment*
Aborted	33	26.2	296.0	36.6%	13.4	1.88	20.4	7.0
Benefitted	32	24.2	156.5	70.9	14.8	3.20	30.6	15.8
Unaffected	33	28.8	114.8	84.8	13.7	4.85	46.8	33.1

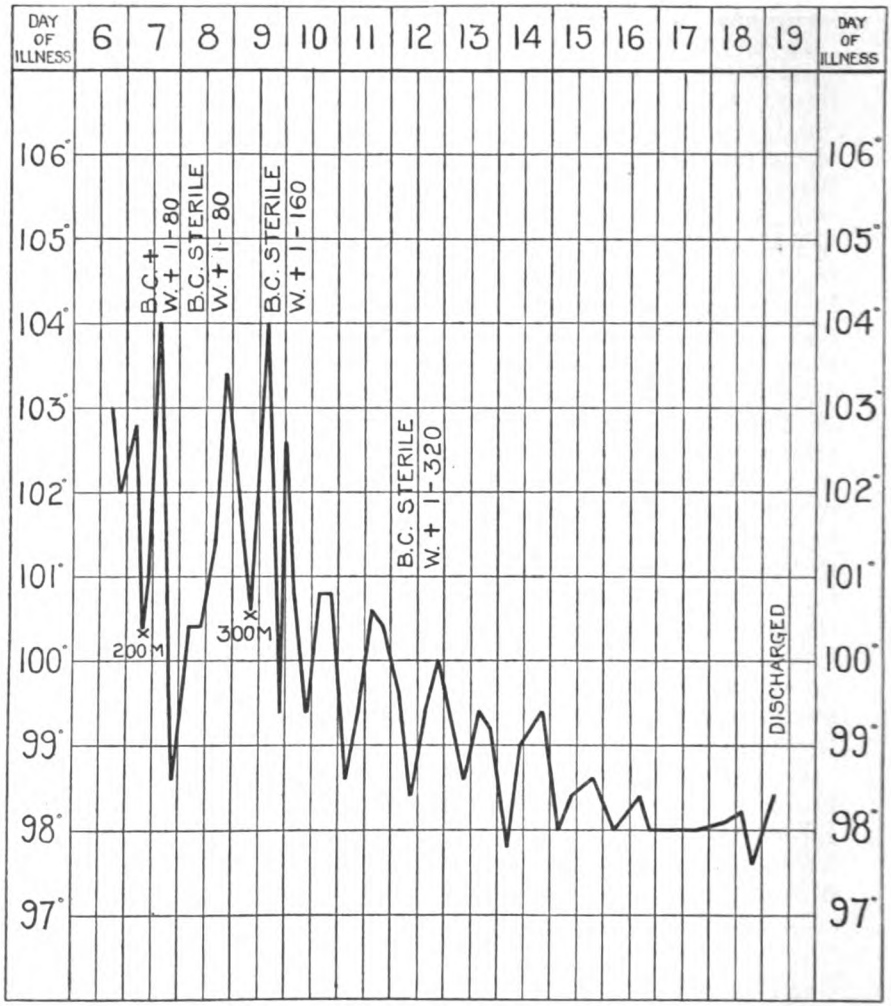

FIG. 4.—Temperature chart in an abortively cured case of typhoid. The temperatures recorded are rectal and give the forenoon and afternoon *maximum* of each day. The mark *X* represents the time at which vaccine injections were given intravenously and the number of million bacteria (200 M) in that particular dose. Above are indicated the results from blood cultures (B. C.) and the strength of the Widal test (W+1–80). Any temperature at or below 100° by the rectum is regarded as normal.

In the first place, it will be seen that our cases may be divided into three almost exactly equal groups in respect to results produced. These groups, moreover, are of almost identical age, and it is also found that treatment was begun on the average at practically the same time in the three groups. They differ in practically all other respects. We find, in the first place, that antibody formation, as evidenced by the Widal or agglutinin titer in the cases before injections were begun, varies markedly in accord-

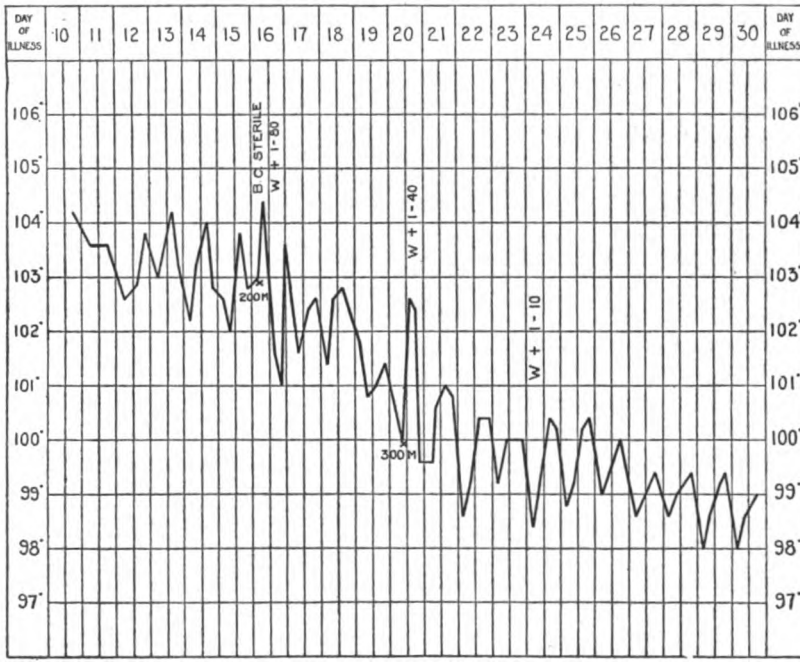

FIG. 5.—Temperature chart in a benefited case of typhoid fever treated by intravenous vaccine injections. Notations as in Chart 4.

ance with the eventual outcome of the case in question. In the abortively cured cases the Widal is found to be on the average over twice as high as in the unaffected cases, whereas the benefitted cases lie intermediate between the two groups. A strong Widal is evidence, then, of a good prognosis, not only in respect to these treated cases but probably also in untreated cases, to judge from the experience of others. Inversely correlative with the strength of the Widal is the occurrence of the percentage of positive blood cultures in the three categories under discussion; whereas the cases

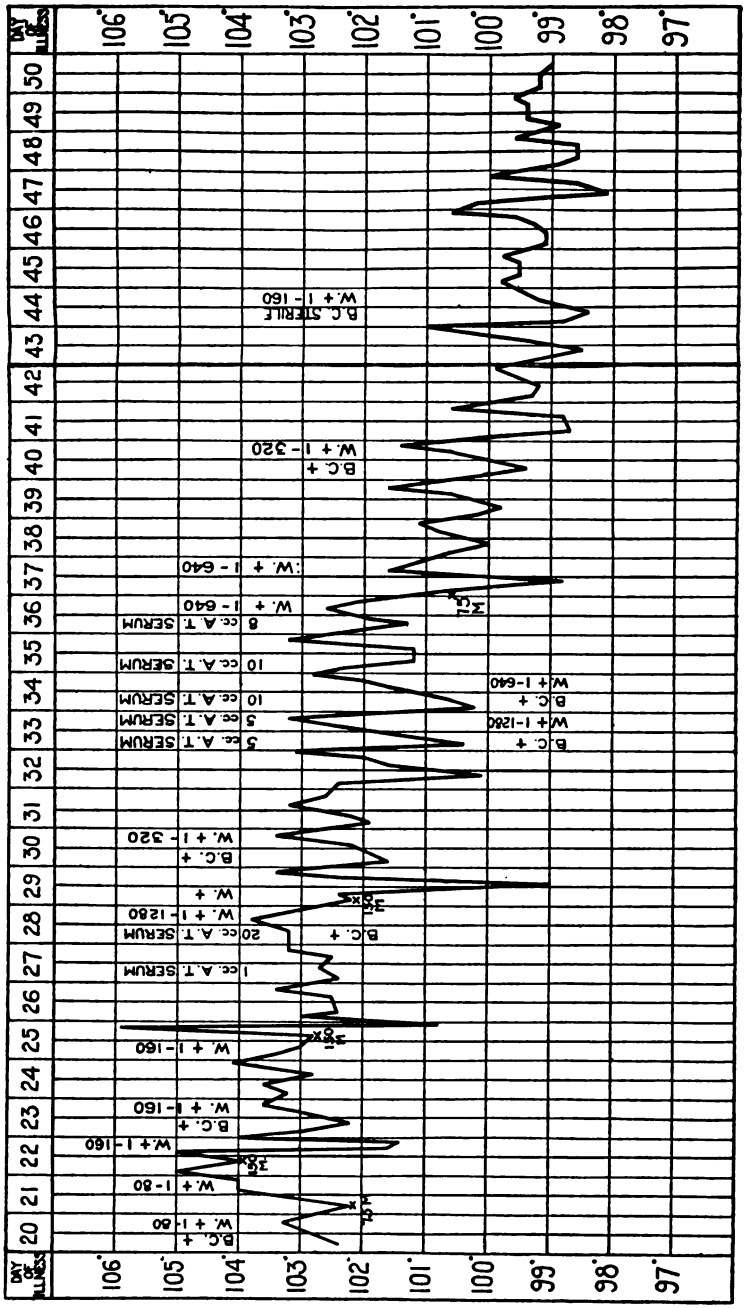

FIG. 6.—Temperature chart in a case of typhoid unaffected by intravenous vaccine injections. Notations as in Chart 4. A. T. refers to an antityphoid serum also given intravenously.

that respond less well to treatment are found to give positive blood cultures in nearly eighty-five per cent of cases, those that recover abruptly on treatment had positive blood cultures in only 36.6 per cent. The benefited cases, again, lie intermediate between the two. These relations between blood cultures and antibody formation we have already referred to as representing a balance established in the patient before intervention between the infecting agent and the resisting power of the host. When the resisting power is strongly developed, a favorable outcome may be more confidently expected.

The group of cases which we have classified as abortively cured or abortively recovered suggest in some respects the mild or abortive typhoid cases which are discussed in most extensive monographs on this disease. The typhus levissimus of Griesinger, the typhoidette of Brouardel, or abortive typhoid forms a well recognized group or groups that must occur in every considerable collection of cases of typhoid fever. Estimates vary as to the exact proportion of such cases, as may normally be expected. It is probable, as Curschmann suggests, that at least two groups should be formed, the mild typhoid fevers and the abortive typhoid fevers, the latter more frequently though by no means invariably characterized by a somewhat abrupt rise and fall of temperature and an abbreviated fastigium. McCrae in his 1500 cases found three per cent of mild forms of the disease, and, in addition, 0.1 of one per cent of his cases recovered by crisis. Letulle found that these two types of the disease occurred particularly in certain epidemics and in children. He finds something over seventeen per cent in the cases of the disease which he collected. This figure may certainly be regarded as an extreme maximum of occurrence. According to Curschmann, the abortive and mild forms frequently have only three to six days of fever and almost never over ten or twelve days, with which statement Hare and Beardsley would agree. At all events, the cases of mild and abortive typhoid together must constitute a relatively small percentage of all, in spite of the figures of Letulle. Hare and Beardsley note that Coleman found only twenty-four such cases in five years' experience at the Bellevue Hospital in New York. At all events, no such number as one-third of all the cases, as in our series, could be found in this way without some type of intervention. It may further be noted that our cases almost invariably have occurred beyond the limit of ten to twelve days set by Curschmann, and have practically invariably been characterized by a critical fall of temperature, and what is more important still, show a direct relation between this critical fall and

the injection of vaccine. Our cases do not represent the mild epidemics of Letulle, nor has any considerable number of them been furnished by children. They have been gathered over three seasons and in widely different localities. As may be anticipated, the abortively recovered cases represent by and large, when estimated before treatment was begun, the milder cases of the disease in this series. Our characterization of a preponderance of these abortively cured cases as milder has no relation, however, to the small group of mild and abortive forms that have just been discussed. We have endeavored to register our impression as to the severity of each case before treatment was begun, and our results are expressed in Table XXVI, where it is found that many more severe cases occur among those that remain unaffected by treatment, and many more mild cases occur among those that are aborted, whereas the benefitted cases would seem to lie intermediate between the two.

TABLE XXVI

GENERAL CONDITION OF CASES BEFORE TREATMENT

	Severe	*Moderate*	*Mild*
Unaffected	26	6	1
Benefitted	10	17	5
Aborted	4	13	16

It is evident, then, that the milder cases react better to treatment than the more severe, but even the most severe ones will in some instances at least be benefited and even aborted. We believe the effects actually produced are best represented by the figures given under "Permanent normal temperature" and "Duration of treatment" in Table XXV. It is found that a permanent normal temperature was obtained in the third of the cases that are called aborted on an average at about the twentieth day. When we consider that the treatment of these cases was not begun until the thirteenth day, the really significant figure of seven days as the average duration of treatment required to restore the patient to an essentially normal condition, so far as the temperature is concerned, is obtained. We find, moreover, that it took on the average a little under two injections to produce this result. The fall of temperature by crisis, which is exemplified in the figure (Figure 4) used to illustrate the abortive cure, is characteristic of this category, although the abrupt fall may not occur in every instance on the first injection.

The benefited cases, again, are well typified in the illustrative

chart (Figure 5); each successive injection of vaccine produces a permanent fall in temperature on the average of one degree, and it may require several, on the average a little over three injections, to reduce the temperature to a permanent normal. The average duration, then, of these cases is found to be 30.6 days, and the duration of treatment the more significant figure, 15.8 days.

The cases that have been listed as unaffected, although showing the ordinary temperature excursions following each injection, are characterized by a prompt return of the temperature to its original or nearly its original height. The impression has remained in the minds of many who have seen those cases that they are really benefited, but since we have taken the reduction of temperature as our criterion of results, we prefer not to emphasize any good effect that may have occurred in these cases, beyond the diminution in complications and mortality, to which we shall presently refer. Even in this group of cases the average duration is by no means extraordinary, 46.8 days, although it does exceed somewhat, perhaps, a normal average duration of cases of typhoid fever. It is extremely difficult to estimate what such an average duration usually is. Curschmann regards the mild cases as lasting on an average of twenty-one to thirty-three days. In McCrae's [7] figures the average febrile period was thirty-one days. It should be noted that our figures refer to the total duration of the disease from its initial symptoms, so far as they can be estimated from the patient's history, and not from the known duration of the fever itself. The group of cases, then, that were best affected may reasonably be regarded as having run a distinctly short course, and the average of all cases, which is about twenty-nine days, is not markedly different from McCrae's thirty-one days.

The mortality in this series of ninety-eight treated cases is 6.6 per cent, which, when we consider that the cases were treated over a period of three seasons under varying conditions of care in private houses as well as hospitals, and, moreover, treated in different parts of the country, is certainly a very satisfactory figure. The average mortality is usually figured at ten per cent. The cases of death were predominantly due to the accidents of typhoid, three to hemorrhage, complicated with perforation in two instances, two to a combination of laryngitis and bronchopneumonia, and one only to typhoid toxemia. It should be emphasized in this connection that treatment was withheld in no case on account of the seriousness of the patient's condition, a fact of significance in considering the low mortality obtained. In two, at least, of our fatal cases the prognosis seemed inevitably

fatal when treatment was begun. The treatment itself in these cases not only seemed to produce no further ill effect, but actually gave rise to a temporary benefit.

The complications, again, were few in number, and only thirteen in all in the entire ninety-eight cases (13.2 per cent). This means, not that thirteen cases showed complications, for there were indeed only eight cases which showed complications, but the total number of complications was thirteen. These complications were as follows: pyelitis one case, lobar pneumonia one case, laryngitis two cases, bronchopneumonia two cases, toxemia one case, hemorrhage four cases, perforation two cases. The percentage of hemorrhage (4%+) and of perforation (2%) is certainly below what may be expected as the usual averages for these complications, five to ten per cent for hemorrhage and three to four per cent for perforation. Although the earlier study of vaccine therapy in typhoid certainly led to the impression, particularly when the vaccine was administered subcutaneously, that complications were diminished (Krumbaar and Richardson, Callison), more recent work would seem to show that no distinct effect on the complications can be expected by the more recent intravenous type of treatment (Szecsy, Wiltshire and MacGillycuddy, Reiter, and Guinon and Malarte).

The occurrence of relapses in this series of ninety-eight cases is of interest in connection with a supplementary type of vaccine therapy, to which Gay and Chickering referred in their communication. It is apparently the experience of several authors, including ourselves, that the intravenous vaccine therapy of typhoid fever, although it may lead to surprisingly successful results in shortening many cases of the disease, is of little value in preventing relapses. In our series of cases there were ten relapses (10.2%), which is approximately the number that might be expected. After experiencing several of these relapses we decided to follow up the intravenous therapy by a series of three subcutaneous injections of 0.1 milligram of the vaccine (800 million bacteria), given on alternate days beginning at the point where the patient's temperature had remained normal for twenty-four hours. Thirty-seven cases in the latter part of our series have been treated in this manner and among them relapses occurred in only 5.39 per cent, whereas in sixty-nine cases in which the intravenous therapy was not followed by subcutaneous vaccine injections the relapses occurred in 11.59 per cent. The same method of treatment has since been recommended by F. Meyer,[2] Meyer and Altstaedt, and Wiltshire and MacGillycuddy.

Non-Specificity of Vaccine Therapy in Typhoid

It has become increasingly evident that the results produced by the administration of typhoid vaccine in typhoid fever cannot be regarded as specific in the narrower sense. The results, however striking they may be, are due primarily to the fact that a foreign protein has been injected more than to the fact that the foreign protein employed is a preparation of the causative agent in the disease in question. In the first place, it has been found that beneficial effects of a very similar nature and characterized by similar reactions to those described have been produced in typhoid fever by the administration of vaccines prepared from bacteria other than the Bacillus typhosus. Kraus was the first to note that he obtained beneficial results on the intravenous injection of colon as well as of typhoid vaccines. Ludke [3] and Lucksch both obtained results with colon vaccine, and the latter author obtained a favorable effect by gonococcus vaccines and by sodium nucleinate. Zupnik, Müller and Leiner have utilized a vaccine made from the mouse typhoid bacillus as less toxic and as useful as true typhoid vaccine. Reibmayr, who has employed colon and cholera vaccines in typhoid as well as typhoid vaccine, concludes that the former, although beneficial, are not as good as that derived from the specific microorganism.

In a similar manner it has been found that other acute infectious diseases may be beneficially affected by the intravenous injection of their corresponding vaccines or of other vaccines. Thus, Kraus [2] notes the beneficial effect produced in cases of puerperal sepsis and pyocyaneus infections by the use of a colon vaccine. Rhein notes the beneficial effect in paratyphoid fever of typhoid vaccine. Nolf utilized peptone solutions advantageously in streptococcus infections. Miller and Lusk have employed typhoid vaccine by intravenous injection in acute, subacute and chronic arthritis with favorable results.

This leads to a consideration of the less complex proteins and, indeed, simple inorganic salts that have been employed with claim to equally favorable results both in typhoid and in other acute infections. Ludke [3] has described the use of deutero-albumose in typhoid, Weichardt the employment of albumin solutions, and Nolf, as already mentioned, has used one-half a gram of peptone dissolved in 200 cubic centimeters of normal saline and administered intravenously. Baradulin has utilized dextrose solutions in considerable amount in cases of surgical sepsis, and Weichardt and Engländer have obtained similar results with

normal physiological saline alone. The use of colloidal gold (Colibiase) by Letulle and Mage, Barachon, Gay, Labbé and Moussaud, and Delbet would seem simply another instance of the non-specificity of the reaction that we have described.

It should be reiterated that in each and all of these instances the beneficial effects produced, which are undoubted, are brought about by the *intravenous* injections of a non-specific vaccine, a less complex protein, or even a complex or simple organic or inorganic substance. These injections, moreover, have all been followed by the train of symptoms we have described with typhoid vaccines, of chill, temperature excursion, and the results in the nature of critical recovery have been similar, though probably differing in relative percentage.

The Mechanism of Cure in Intravenous Vaccine Therapy

This proof of the non-specificity of the most favorable results that can be produced by a typhoid vaccine in typhoid fever should not only not discourage us but lead us to inquire further into the mechanism of the reaction on which this benefit depends. In our work (Gay and Claypole,[4] Gay and Chickering) we have been led to attribute significance to two factors, which we believe not only concerned but of importance in the reaction which is produced by intravenous vaccine injections. The first of these factors is the hyperleucocytosis which following our observations has also been found to occur by a number of authors (McWilliams, Holler, Löwy, Lucksch and Wilhelm, Lucksch, Rohonyi, and Scully). It has also been shown that many of the substances which in a non-specific manner may lead to the same effects, as, for example, nuclein (Melnikowa and Wersilowa), and colloidal gold (Busquet, Barachon, Letulle and Mage), also increase the leucocyte count, to which fact their results have been attributed.

As a second factor on which the degree of benefit obtained would seem to depend is the antibody content of the patient. This is indicated in the results cited in Table XXV, where it is found that the strength of the Widal titer seems to increase directly with the benefit that results from injection. This observation, moreover, would agree with the incidental observation of a number of observers that prognosis in general is more or less dependent on the strength of antibodies in the patient, and, particularly, that the prognosis of vaccine injection likewise bears some relation to the degree to which the individual has reacted against the infection. Of like significance is the extremely mild

and favorable course of typhoid fever in the vaccinated. Koranyi has found that the opsonic index rises after vaccine injection in typhoid, and Inez Smith in our laboratory has apparently been able to demonstrate a distinct relation in the degree to which the opsonic index increases after intravenous injection and the result produced. In other words, the opsonic index rose much more markedly in the cases that were abortively cured than in either the benefitted or the unaffected cases. We have also frequently found that the agglutinin titer rises after the vaccine injection.

Our hypothesis as to the mechanism by which cure was effected in the most striking instances has been, briefly, that it was due to a coöperation between the leucocytes that were called out by the injection and the antibodies already present in the patient, which latter substances acting as tropins caused the digestion and destruction of the typhoid bacilli in the body by the increased white blood corpuscles. There are several reasons for regarding this mechanism as probable apart from the now proved relation of the antibody strength and the leucocytic increase to the result obtained. In the first place, it can be shown by blood culture in some, though by no means all, instances that the bacteria disappear rapidly from the peripheral circulation following the injection. Similar results have been obtained by other investigators. This working hypothesis may or may not be the correct or ultimate explanation of the results produced by this nonspecific reaction in typhoid fever and in other acute infections. There are other explanations which are probably no more ultimate and which, indeed, are not of necessity in any direct conflict with the one we have presented. Jobling and Petersen have attributed the results produced by the reaction as due to a disturbance of ferment, antiferment balance, the antiferment being absorbed and the ferment being allowed to act. Similarly, Nolf speaks of a change in colloidal balance. This explanation is certainly a very attractive one. Teague and McWilliams [1, 2, 3] in recent experiments on rabbits also bring forth certain results which must be taken into consideration in explaining this type of therapy. They find that the injection of vaccine in rabbits produces a refractory condition which renders these animals temporarily more resistant to infection with the typhoid bacillus. They would attribute the results produced in the favorable cases of treatment to an overflowing of bactericidal substances, which are found to be present in the circulating blood, into the remoter lymph spaces which serve as metastatic foci in typhoid fever,

and the consequent destruction of the bacteria that are present in them.

It makes very little difference whether we regard the leucocytes or bactericidal ferments in the serum as the cause of the ultimate destruction of the bacteria, with which recovery seems to be associated. It is probable, indeed, that the white blood cells are the source of the ferments, and we see no reason why these various factors and experiments that have been brought out by Teague and McWilliams, Jobling and Petersen and ourselves will not eventually stand in harmony in the ultimate explanation which may soon come.

Since the cases in which the least favorable results are obtained seem characterized by the low antibody content in the serum, Gay and Chickering suggested that better results might be obtained in them by supplying the deficient antibodies by injections of an artificial serum, and reported one or two cases in which a preparatory injection of the serum of a goat that had been immunized by repeated injections of typhoid bacilli seemed to render the beneficial results secured by subsequent vaccine therapy more pronounced. Further limited experience with various antisera from goats prepared both by the injection of sensitized and of unsensitized living cultures (Gay [3]) would not seem to give the anticipated result. The injection of an antityphoid serum of this sort may in itself produce a reaction similar to that evoked by vaccine (Étienne), and it is probable that the effect produced by Rodet and his collaborators, to which we have already referred, is, in part at least, due to the fact that a foreign protein has been employed, since their results were better when the vaccine was given intravenously. The possibility, however, of a combined serum and vaccine therapy is one which we believe should be kept in mind and more extensively tested.

Inasmuch as similar therapeutic results to those described following the use of typhoid vaccine can be obtained by the intravenous injection of almost any protein substance, the question may well be asked as to whether there is any advantage in using typhoid vaccine rather than some other substance. We believe that a typhoid vaccine, particularly of the type we have recommended, possesses distinct advantages over other proteins. Such a vaccine, as we employ it, is easily kept indefinitely in dried form and under conditions of strict asepsis, and can readily be introduced in exact amounts. Typhoid vaccine, further, has the advantage over other protein preparations of building up the active immunity of the patient, and a sensitized vaccine

will in our experience produce a higher grade of leucocytosis. It is evident from remarks we have made that in our own experience the use of typhoid vaccine intravenously is attended by no real danger and is contraindicated in only those few cases of typhoid fever which are complicated by some profound functional disturbance of the heart. The very few individuals who have been led through unfortunate experience to discontinue the intravenous injection of vaccines, Peutz, Sladek and Kotlowsky, and Deutsch, treated very few cases, and the dangers which they report must be attributed to their inexperience and the excessive amount of vaccine employed. We regard, then, the intravenous vaccine treatment of typhoid fever as the most effective type of therapy hitherto devised to combat this disease. It would seem indicated in nearly every case and at any time during the febrile period. It would seem, moreover, likely that further investigation will enhance the value of this type of therapy.

CHAPTER XIV

SUGGESTED METHODS OF ADVANCE IN SOLVING THE TYPHOID PROBLEM

An attempt has been made in this treatise to express the present status of our effective knowledge concerning typhoid fever. Matters of apparently purely theoretical interest have been treated as fully as those with a practical application, with an appreciation of the fact that such theoretical knowledge will eventually serve directly or indirectly in the practical advances that are to come. It is evident that increasing knowledge of the mechanism by which typhoid fever propagates itself, both within and without the human body, has given us increasing power to diminish the incidence of the disease. As we have shown, both the morbidity and mortality rates from this disease have been enormously reduced, and the reduction continues. This reduction in the incidence of typhoid fever in the larger centers of population is due largely to the appreciation and enforcement of sanitary measures carried out with a thorough knowledge of the life cycle and distribution of the typhoid bacillus. In smaller groups the more recent and effective advance has been in the matter of immunization in conjunction with the ordinary sanitary precautions. Vaccination against typhoid, although extremely effective in segregated and particularly in completely immunized units, has not so far exerted a fundamental effect on the total morbidity rate from the disease. The advances that have been made in the suppression of typhoid fever cannot but awaken confidence and enthusiasm in the effectiveness of preventive medicine. These advances have been so marked in the case of this disease that we may confidently look forward to its eventual suppression. This suppression will be brought about both through the consistent application of measures arising from the knowledge we already possess as to the pathogenesis and transmission of typhoid fever, and through the acquisition of further knowledge of certain aspects of the disease. It is the purpose of these closing paragraphs to attempt to outline certain paths along which may come these advances in our knowledge of typhoid fever and in its control.

THE DIAGNOSIS OF CASES OF TYPHOID FEVER

One of the most important factors in preventing the extension of typhoid fever lies in the early detection of each individual case. The methods of diagnosis of typhoid fever are so highly perfected that diagnosis can be made at least in the earliest days of the disease, and, indeed, might be made in the incubation period of the disease, if suspicion were directed toward the individual in question. The early diagnosis of typhoid fever depends not only on the cooperation of the laboratory with the practitioner of medicine, but on the willingness and initiative of the practitioner in availing himself of such coöperation as is available. It should be the function of the laboratory not only to accede to the demands of the practitioner but to suggest methods of which the practitioner might and should avail himself. In every well organized community facilities are at hand for the free diagnosis of blood samples by means of the agglutination test for typhoid fever. These means are made use of by all well informed practitioners and their aid in diagnosis and in protecting the public health is very great. The early diagnosis of the disease is obtained, however, as we have shown, more surely by means of blood cultures, and this method of diagnosis is by no means as available as it should be for the general practitioner. The practitioner has usually neither the experience nor the facilities for making and particularly for studying blood cultures, and it should be the duty of every municipal and state laboratory to afford greater facilities, not only for the detection of the typhoid bacillus in blood cultures, but for the actual taking of the cultures themselves. A simple extension of the district nurse system, in cities at least, would provide for this deficiency in the diagnostic aid that is furnished by state and municipal laboratories. A trained nurse could readily be instructed in the complete technique of obtaining and diagnosing blood cultures, and the additional expense to the community would be inconsiderable.

THE MANAGEMENT OF CARRIERS

We have sufficiently emphasized the importance of carriers as a means of the further extension of typhoid fever. This method of extension is due in large part to the fact that carriers are unsuspected. If all carriers of typhoid bacilli were known, the first and most important step would be made in preventing the genesis of secondary cases from this important source. Every effort should

be made, particularly in densely populated communities, to obtain as complete a registration of carriers as may be possible. This may be effected in several ways. In the first place, every recovered case of typhoid fever should have several negative stool examinations before being discharged as healthy. Provision should be made so that such examinations may be carried out not only in hospitals, where at present they are infrequently performed, but also in private cases through coöperation between the attendant physician and municipal laboratories. Recovered cases that remain carriers would thus be detected and recognized. Their recognition would in most cases in no way interfere with their personal liberty, but would make it possible for a central laboratory to keep in touch with them. Careful instruction should then be given to all such carriers and every effort made to teach them to appreciate their potential danger to the community. If such carriers would sign an agreement to report to the central laboratory for examination, their eventual freedom from typhoid bacilli might be determined. More important still, their relation to any further cases of the disease would be promptly discovered and means taken to prevent additional infection. Legal measures should be available to enforce the compliance of these recovered carriers with such rules as may be laid down for their conduct, and isolation, even, should be possible in recalcitrant or careless individuals.

Thorough-going search for and registration of all recovered carriers will lead eventually to the complete census of all sources of further infection in this category. Such methods, however, will not aid in the detection of carriers who have come from less closely guarded communities, or of the healthy carriers in a most carefully checked community, such as we have outlined. We have already expressed the difficulty or impossibility of detection of all carriers in any general community by the laborious methods of stool examination which at present are necessary to find them. It is increasingly evident that some easier method of detecting typhoid carriers is highly desirable. So far, the only possible test pointing to possible carriers rests on a positive Widal reaction, which, however, is not present in all carriers and is positive in many who are not carriers. The suggestion is made that the possibility of employing the typhoidin test for the purpose of detecting healthy and recovered carriers should be investigated.

Most important from the public standpoint, next to the detection of carriers, and more important still from the individual standpoint, is some means of treating them effectively. We have fully considered how inadequate all suggested methods of cure

have been. Further study of the rabbit carrier condition, which presents so close an analogy to the human carrier, is obviously indicated. The possible use of chemotherapeutic means of effecting this end by studying the elimination of various dye stuffs and chemical substances through the liver and bile have already suggested certain studies with this purpose in view, and definite progress may soon be made in the direction of some specific method of curing the carrier condition.

IMMUNIZATION AGAINST TYPHOID FEVER

Further practical advances are possible in methods of vaccination against typhoid fever, and theoretical studies as to the nature of the immunity produced by vaccination will doubtless serve toward these advances. We may well question why the protection afforded by vaccination in recognized manners against typhoid fever is less durable than that accomplished through recovery from the disease. We have already outlined the differences in the expression of this immunity in the blood serum in the two instances and expressed the opinion that recovered typhoid immunity is cellular, whereas artificial typhoid immunity is to a large extent humoral in nature. The exact nature of this durable cellular immunity acquired through recovery is by no means understood, and an intensive comparative study of the tissues in recovered typhoid cases as compared with those vaccinated against typhoid and with normal individuals might afford some information in this direction. If it could be demonstrated, for example, that certain tissues of recovered typhoid cases, perhaps the tissues of the lymphatic system, contain cellular antibodies in contradistinction to normal tissues, great insight as to the nature of this durable immunity would be gained. Whether it is possible to produce a fundamental immunity of this sort by artificial means is extremely doubtful, but at least an appreciation of the differences between this type of immunity and that afforded by vaccination might be expected to aid in further perfecting the latter process.

Every effort should be made to stimulate typhoid vaccination in the general community. This may be brought about by propaganda of various sorts and by the free distribution of vaccine by municipal, state or even federal laboratories. The inclusiveness of vaccination would seem to increase its efficiency, and every effort should be made to create a typhoid vaccinated community in such a manner as has been done in the case of small-pox.

In addition, further investigation is desirable as to the duration

of protection by any method in vogue. We have already suggested the value of the typhoidin test as indicating the failure of individuals to respond sufficiently to the vaccine to ensure normal protection, and some systematic method of applying this test, if it proves as reliable as we have anticipated, should be considered.

TREATMENT OF TYPHOID FEVER

The greatest progress that has been made in the treatment of typhoid fever would seem to be in connection with the protein reaction produced by the intravenous injection not only of typhoid vaccine, but of other protein substances. The nature of this reaction is to some extent understood. The relation of leucocytes to the process and the stimulation or mobilization of antibodies induced by this means are recognized. Of the theories that have been advanced to explain the beneficial results that not infrequently follow this injection of foreign protein, the most attractive would seem to be that of Jobling and Petersen, which is fully in harmony with the ideas of Nolf and others as to fluctuations in the colloidal balance between ferment and antiferment. It would seem desirable, not only for practical ends in connection with protein therapy of this type, but for the purpose of theoretical knowledge that better methods of detecting and complete demonstration of the presence and nature of such ferments should be available. It is particularly desirable from the standpoint of general considerations of immunity that further knowledge should be obtained as to the relation of ferments of this sort to recognized types of antibodies that have been more circumstantially studied.

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